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EDITED BY

CRIGHTON BRAMWELL
O. L. V. S. DE WESSELOW
A. W. M. ELLIS

F. R. FRASER
D. HUNTER
J. W. McNEE

WITH THE HELP OF

E. FARQUHAR BUZZARD
GORDON HOLMES

ARTHUR F. HURST
J. A. NIXON

R. A. PETERS
E. I. SPRIGGS

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POLYPS OF THE STOMACH AND POLYPOID GASTRITIS¹

By EDMUND I. SPRIGGS

With Radiography and Drawings
by O. A. MARXER

(From Ruthin Castle)

With Plates 1 to 8

Introduction

FROM time to time filling defects caused by pear-shaped or nodular masses are seen in the stomach on X-ray examination with barium. These masses differ from malignant growths in that usually they have a smooth outline, interfere but little or not at all with the peristalsis or contraction of the stomach wall, and are unaccompanied by clinical signs of gastric carcinoma.

THIS is 121 years since we began to use and develop the present method of

IMPORTANT NOTICE TO INTENDING CONTRIBUTORS

Owing to paper restriction the length of future numbers of the journal will be severely limited. Intending contributors are therefore urged to make their MSS. as short as possible.

of stomachs examined. In seven cases; in an eleventh case, the polyp, revealed at operation, was in the duodenum. The second class includes polypoid outlines, usually multiple, due to hypertrophic oedematous folds holding barium deep in their recesses. These are nearly always of a different radiological and gastroscopic appearance. The so-called hypertrophic gastritis is fairly common; only those cases are included here which showed large nodular masses, and of these there were 19. In the same period a diagnosis of gastritis was made in 470 patients.

The cases seen in one clinic are here considered from a physician's point of view. Several of them, observed over years, have not come either to operation or autopsy. Cases with a clinical history are also taken into the record which have been communicated by the kindness of interested colleagues and the curators of pathological museums in this country, to whom we are deeply indebted. These cases are tabulated in the Appendices with acknowledgement of the source, together with 24 pathological specimens

¹ Received July 2 1942.

which a clinical history is not available. Many interesting specimens have been lost through enemy action.

In the following pages the words 'our own cases' or 'our own series' refer in Part I (polyps) to our own cases, nos. 1 to 11, described in detail in the text, and in Part II (polypoid gastritis) to our own 19 cases which are tabulated in Appendix G. These 30 cases are the basis of the present study. The after history of each is known. The words 'the whole series', used mainly in Part I, refer to our own 11 cases plus the 34 cases (polyps) with a clinical history, tabulated in Appendices A and C; or, in some instances, which are made clear in the context, to our own 11 cases plus all the 59 cases in Appendices A, B, C, and D, that is, including the pathological specimens without a clinical history, a total of 70 cases. All the cases, except four, are, so far as the writer's knowledge goes, hitherto unpublished.

The cases are numbered as follows:

PART I. POLYPS			No. of cases or specimens
Our own cases 1 to 11, described in the text, pp. 15 to 20			11
Epithelial tumours, single or a few, Cases 12 to 26	Appendix A		15
Epithelial tumours, single or a few, pathological specimens with no history		B	13
Polyposis, with history, Cases 27 to 35		C	9
Polyposis, specimens without history		D	9
Leiomyomata, with history, Cases 36 to 46		E	11
Lipomata		F	2
			<hr/> 70

PART II. POLYPOID GASTRITIS

Hypertrophic gastritis, our own cases, after ulcer or operation, Cases 47 to 53		G	7
Hypertrophic gastritis, without preceding ulcer or opera- tion, Cases 54 to 65		G	12
Hypertrophic gastritis, specimens with history, Cases 66 and 67		H	2
			<hr/> 21

The totals are:

Polyps, 46 cases with a history and 24 pathological specimens with none, that is, 70 cases.

Polypoid gastritis, 21 cases with history.

The considerable literature upon benign tumours of the stomach was first written from the pathological aspect, the growths being found *post mortem*; secondly, when abdominal surgery developed, they were revealed from time to time at operation. Latterly, valuable papers have appeared from the radiological and a few from a clinical point of view. In summarizing symptoms in Part I, 54 cases in the literature are also taken into account from 21 authors who give details about their own patients. These added to our 46 cases make 100 cases in all of polyps with a clinical history. The literature of the massive swellings occasionally seen in hypertrophic gastritis is scanty. This condition, which is less obvious at autopsy and especially

after post-mortem digestion, is described in Part II. In one group of the cases, namely those associated with ulcer and about a gastro-enterostomy, tumefactions of the mucous membrane are seen at operation. In others they have been mainly unrevealed in the living until radiology or the gastroscope, or both, have shown them. Our experience is in agreement with that of Eusterman and Morlock (1939) that polypoid forms of hypertrophic gastritis have to the clinician much in common with polypoid gastric tumours.

Definition. The word polyp means many-footed and was applied to the cuttlefish. In zoology by 'old or careless usage' other invertebrates having a resemblance to the true polyps were also thus named. In medical writings the polypus of the nose is mentioned by Celsus early in the first century A.D. The term has come to imply a pedunculated tumour, and especially small tumours in hollow channels, such as the nose or alimentary canal. There is, therefore, no unity in the term polyp (Borrmann, 1926), since it includes genuine growths, hyperplasias from chronic irritation, and such oedematous formations as nasal polypi. Sessile and even flat lesions of similar pathological nature are included. The term polyadenoma is used for many adenomata, not easily counted, in the same stomach, and the more general term polyposis for many polyps of any structure.

History. Amatus Lusitanus (1557) is said to have described a gastric polyp. It is a dramatic story, but the diagnosis is not clear and there is no account of an autopsy. Morgagni (1761), who missed so little, wrote that in the stomach of a woman of 50 years who died of dropsy, near the pylorus 'was a pretty large earuncle, fix'd, by an oblong stalk, to the internal coats, and of the same colour therewith, if looked at externally; for internally it was made up of a soft substance, that was red, but degenerating into white'. He also described what was probably a myoma, in a woman of 70 years, projecting from the posterior surface of the stomach (Alexander's translation, 1769). Cruveilhier (1835) described polyps and the harm which they can do by becoming malignant or by blocking the pylorus, also multiple polypi, with a picture in his Atlas. Quain, in 1857, reported to the Pathological Society of London the case of a girl of 19 years, of robust appearance, who had complained of pains after food and in the night. She felt faint and vomited a tumour of the size of a chestnut, with a small pedicle. As symptoms continued it was thought likely that there were others. The tumour was covered with columnar cells. This was the first recorded time, so far as my reading has gone, that a diagnosis was made, or rather made itself, during life. Rokitsansky (1861) in his textbook described gastric polyps, and in 1864 a detailed paper appeared by Ebstein who related eight cases already published and added 16 more.

In 1888 Ménétrier gave to the Anatomical Society of Paris his classical paper on gastric polyadenoma. With French clarity he describes the irregular glandular proliferation, with cyst formation, of small adenomata, describing them as developed from the mucosa by a circumscribed hypertrophy, and

movable upon the lower layers. Two cases are quoted of this *polyadenome polypeux* and one of a single polyp. He described the change of the gland elements to goblet cells, producing mucus, and to cells of a functionally undifferentiated character. Not a great deal of descriptive value about polyadenoma has been added to his paper. Ménétrier also described as *polyadenome en nappe* longitudinal swellings in the stomach, more general and diffuse, looking like convolutions of the brain. He remarks that these are rarer, and are usually put 'dans la groupe assez confus de gastrites chroniques'. From the account of the two cases, especially the second, in which the folds were 2 to 3 cm. thick, it seems to the present writer that they do belong to that group, for the histology as illustrated in his paper shows hypertrophy of the mucous membrane rather than adenomatous proliferation, and is similar to that in the gastritic hyperplasia of which sections are shown below. This does not deny the existence of *polyadenome en nappe*. A case in which the mucous membrane is replaced by a flat cloth-like thickening made up of closely packed adenomata may be so described.

Another instance in which, like that of Quain (1857), the diagnosis was made during life was reported by Wegele (1908). On withdrawing a sound from the stomach of a woman of 59 years, who suffered from biliary colic, there was found in the eye of the tube a piece of tissue which had an adenomatous structure. When the gall-bladder with its stones was removed the stomach was opened and the surface found to be covered with soft polyps. A gastro-enterostomy was done for fear of pyloric obstruction. Eighteen months later the patient was thinner, but showed no tumour or cachexia. Myer (1913) in 1909, and Chosrojeff (1912) were also able to recognize polyposis from a piece of tissue in a sound.

This brings us to modern times, for on 7 December 1911, Heinz (1912) reported to the Medicinische Gesellschaft at Bâle that in a man, in whose stomach wash-out a piece of adenoma had been found, a many-processed shadow hanging by a stalk from the lesser curve had also been seen by an X-ray with bismuth. At operation by de Quervain three adenomatous polyps were removed. In the following year, 1912, the first X-ray film of gastric polyps which I have seen reproduced was taken in Myer's patient, who was perhaps the most fully observed and reported case of polyadenoma, from the first complaint of indigestion to severe haemorrhage after eight years, recovery, and later death after operation. In 1913 were reported Stewart's case of polyadenoma associated with cancer and two cases of Meulengracht's in which the stomach had been fixed by the injection of formalin immediately after death. Meulengracht (1913) used the term gastritis polyposa and brought careful histological evidence to support the view that the polyps were the result of a chronic gastritis. This may be so, but there is advantage in that neither Ménétrier's (1888) purely descriptive term of polyadenoma nor the more general term of polyposis brings into the title the problem of causation, upon which pathologists have not been of one opinion. The paper of Eusterman and Senty, with radiology now playing

an adequate part, appeared in 1921, followed by those of Rosenbach and Disqué (1923) and other writers, many of whom are referred to in later pages. The larger single tumours, which are more important clinically than the rare polyposis, began then to be detected by X-rays and to receive the attention of clinicians.

Pathology and histology. Benign gastric tumours may occur in the stomach from a number of pathological states. They include papilloma, adenoma, leiomyoma, adenomyoma, neuroma, angioma, lipoma, angio-endothelioma, and cysts. Of these and other possible varieties some are very rare. Gastro-liths and other bezoars, or masses of hair or vegetable residues, and various foreign bodies have also been detected radiologically. The main or most usual forms of polyps or polypoid tumours fall into three groups, namely, papilloma or adenoma, leiomyoma, and polypoid hyperplasia ascribed to chronic irritation.

1. The papilloma or adenoma may be single or multiple, stalked or sessile; sometimes there is a tufted surface and a tree-like appearance. The size is usually small, occasionally as big as a walnut, though a few large ones are recorded. With the naked eye it may be hard to distinguish small adenomata, which are genuine growths, from hyperplasia of the mucosa. They may co-exist (Case 34, p. 16) and intermediate forms are found (Stämmeler, 1924).

Microscopically there is proliferation of the epithelium and of the connective tissue in varying degree; the latter may be mostly fibrous with few cells or may be oedematous, the former may show grades of mucoid degeneration. The glands may be irregular or in ordered acini (Plates 1 and 3, Figs. 7 and 24), their cells smaller than normal and more cubical, and the membrana propria ill-developed. Obstructions and cystic swellings may be seen. The functioning gastric gland-cells tend to change to a primitive vegetative type. The affected area is usually clearly marked off from the adjacent healthy tissue and inflammatory processes are absent or slight. The muscularis mucosae may be split up and enter the growths (Plate 3, Fig. 24). When polyps become pedunculated the stalk commonly contains no tumour tissue, but is composed of drawn-out mucosa and submucosa.

The mucous membrane away from the polyp may be normal or it may show an atrophic gastritis, with reduction of gland tissue and achlorhydria. Rodgers (personal communication) describes polyps seen through the gastroscope as occurring mostly in stomachs showing mucosal atrophy with anaemia, and on occasion in pernicious anaemia, with which Ungley (personal communication) agrees. No case of pernicious anaemia is recorded in the present series. In some cases adenomatous changes like the polyp are seen in the surrounding mucous membrane with hypertrophic crypt epithelium (Faber, 1935).

The epithelial element of the polyp may become carcinomatous (Plate 1, Figs. 7 and 8). This liability is less in gastric than in intestinal polyadenoma. If there are several or many polyps it is very unusual for more than one area to develop malignancy.

Two varieties of polyposis, as defined on p. 3, can be distinguished, (1) true adenomata, or polyadenoma, (2) polyps formed by hypertrophy of the mucosa in gastritis, gastritis polyposa. This distinction agrees with the statement of Muir (1941) that polyposis may be neoplastic or inflammatory. The former type probably carries the greater risk of malignancy. Thus the cases of Cruveilhier (1835), Ménétrier (1888, No. 1), Wegele (1908), Chosrojeff (1912), Meulengracht (1913, No. 1), Myer (1913), Eusterman and Senty (1921), Mills (personal communication), Rosenbach and Disqué (1923) and Benedict and Allen (1934) probably comprise true adenomata, as does our own early example (Case 2); whilst those of Meulengracht (1913, No. 2), Hurst and Stokes (1926), Faber (1935), Strauss, Meyer, and Bloom (1928), and possibly Davis (1940) may be mainly inflammatory, gastritis polyposa. In some others the histological description is not definite enough for classification.

2. The leiomyoma or smooth-muscle growth is not included by some writers among the polyps, but clinically and radiologically the tumours are similar. We owe to French writers most of the early knowledge of benign gastric tumours, and of those, Debove and Rémond (1893) remark that a myoma finishes by forming a veritable polyp. Leiomyomata are usually single, mostly small, of the size of a pea or cherry, or flat and button-like (Stewart, 1929). Sometimes they grow much bigger and it is these that are met with clinically. They may be typically polypoid within the stomach or may project from both mucous and serous surfaces as in Case 3 in the present series (Plate 4, Fig. 11), or they may be wholly serous as in Case 37 of Sir Robert Kelly, p. 27, or intramural, as in Case 46 of Prof. Learmonth, p. 54. (Henke and Lubarsch, 1926; Christopher, Benjamin, and Sauer, 1941).

On section they are pale and firm, with a fibroid or 'shot silk' surface like a uterine myoma. The obvious origin is from the muscle of the stomach, but there is evidence that some have arisen from arterial muscle. These growths tend to become sarcomatous, as in Case 3 (Plate 1, Figs. 13, 14, and 15). They are liable to ulcerate, often deeply, with resulting gross haemorrhage, and may undergo cystic degeneration or calcification. A myomatous diverticulum has been reported (Lauche, 1924) and a leiomyoma of Meckel's diverticulum has been known to perforate (Koucky and Beck, 1941).

Adenomyoma also occurs in which there are glandular elements from the stomach itself, or, near the pylorus, of Brunner's gland structure and patches of pancreatic tissue, with ducts and islets, the whole intermingled with unstriated muscle. These are epithelial heterotopias (Nicholson, 1923; Lauche, 1924; Taylor, 1927) which probably arise from embryonic rests. Four cases out of 5,700 autopsies were found by Stewart (1929), and Stewart and Taylor (1925) had already described and illustrated four clinical cases not seen radiologically. These were treated successfully, three by partial gastrectomy and one by excision. Three of the cases had been diagnosed clinically as malignant.

3. The hyperplasias are usually the result of a chronic gastritis which, though often causing atrophy of the mucous membrane, at times gives rise

to hypertrophic polypoid masses of various form. The folds or rugae are enlarged, looking pressed together like the convolutions of the brain, as Ménétrier (1888) remarked from post-mortem specimens (Plate 8, Figs. 36 and 37) and as is now seen with the gastroscope. The colour varies according to the intensity of the gastritis. In an acute or subacute state it is red and injected as shown in Plate 1, Fig. 41, and may show haemorrhagic and purulent specks, or in more severe cases, not here considered, erosions, ulceration, or necrosis. In the large chronic oedematous swellings the colour is paler with mucus lying on or between the folds.

Plate 1, Fig. 39, from the gastroscope may be compared with the radiograph of the same case (Plate 5, Fig. 38).

With the microscope the picture is that of a drawn-out inflamed mass of longer and often broader crypts and glands with a normal membrana propria and muscularis (Plate 3, Fig. 33 and Plate 2, Fig. 34). The epithelial cells on the surface and those lining the crypts, including even the chief and parietal cells of the fundal mucosa, are replaced in areas small or large, by intestinal-type goblet mucus-producing and Paneth cells, a metaplasia or acquired heterotopia (Plate 2, Fig. 35). There is a reactive increase of gland tissue which also contributes to over-secretion of mucus, but the glands do not become so irregular, 'snake-like', and cystic as they do with an adenoma, or if any glands are obstructed that is ascribed to connective tissue overgrowth. The crypts contain a purulent mixture of mucus and leucocytes, which also lies upon the surface. An important difference from a polyp is that the hyperplastic area is not sharply marked off from the neighbouring tissue.

The aetiology of two kinds of overgrowth of mucous membrane, namely adenoma and inflammatory hyperplasia, has been a matter of discussion. An irritative origin for gastritic hyperplasia is often obvious. The adenoma is regarded by many, perhaps by most authorities, as a congenital tumour, or as arising from cells which have retained embryonic properties which are usually lost, especially that of over-proliferation or of genuine neoplasia (Stämmeler, 1924). On this view inflammatory reactions around such tumours are ascribed to mechanical injury. Borst (1902) wrote of a congenital disposition to react to stimuli in a way which normal tissue does not. An earlier, opposing, view (Versé, 1909; Lubarseh, 1926) is that the adenoma, and carcinoma, arise from gastritic processes.

Versé (1909) described, from three cases observed *post mortem*, the genesis of polyps upon the folds of hypertrophic gastritis. His account of the dark red colour of a cherry-sized lump seated on a fold and of the microscopical picture gives the impression of the humps and aberrant folds seen in such cases with the gastroscope. Polyps seen gastroscopically are usually associated with atrophic, not hypertrophic gastritis (Schindler, 1937; Rodgers, 1938). Nevertheless Versé (1909) related that a similar polyp perched upon a broad fold of mucous membrane had become a carcinoma, a change which is a feature of true adenoma. The fact that inflammation is usually general and growths circumscribed, he explained by suggesting that the irritation

stimulus is greater at the crest of a swollen fold, leading to proliferation there; if later the catarrh lessens prominences are left as polyps. Meulengracht (1913) gave a similar explanation of the origin of polyps which were definitely adenomata. With gastritis strongly proliferating crypts build a small prominence. The next step is that, since there is no room for further growth, such little heaps are pressed together, lift the mucous membrane, dragging the muscularis mucosae with it, and a peak is formed, all the elements for a developed polyp being then present.

The objection that a common result of gastritis is atrophy of the mucous membrane is met by the view that inflammation is also the cause of a reparative hyperplasia, atrophic-hyperplastic gastritis (Konjetzny, 1938; Faber, 1935), which leans to neoplasm; intermediate stages and combinations are seen as in Case 34, p. 53 and Plate 1, Fig. 46. This does more to explain the rare polyadenoma than the more frequent occurrence of one or a few polyps upon an apparently normal stomach lining, as seen with the gastroscope (Schindler, 1937), the appearance of hypertrophic gastritis being usually entirely different (Plate 1, Figs. 3, 4, 39, 40, 41).

Much experimental work has been done with the object of inducing stomach tumours in animals, in order to shed light upon their causes. Fibiger's (1913) interesting research seemed to establish that in rats infection with a nematode parasite of cockroaches gave rise to polyps of the squamous epithelium of the stomach. Superimposed malignancy and metastases were also described. This supported the suggestion that gastric papillomata are like infective warts. The conclusions drawn, however, are not confirmed by Passey (1935) and Passey, Leese, and Knox (1936) who repeated the experiments; dietary deficiency has been found to be followed by overactivity of epithelium (Wolbach and Howe, 1925; Fujimachi, 1926; Hoezel and Da Costa, 1931); and the apparent secondary growths in the lungs were due to metaplasia, to which these animals are liable. Klein and Palmer (1941) in a review of experimental work, including that of Cramer (1937) who describes an 'erratic development' of such tumours, conclude that whilst parasites can aggravate mucosal changes, the growths may be due to other conditions not satisfactorily eliminated. Local growths can also occur after mechanical or chemical irritation or stimulation (Bullock and Rohdenburg, 1918) such as that of various carcinogenic substances (Twort and Bottomley, 1932).

In any case only the pyloric part of the stomach of the rat, and not the squamous fore-stomach, is comparable to the glandular mucous membrane of the human organ. Benign polyposis of the rat's glandular stomach is much less common, though it has followed some experiments (Waterman, 1936; Roffo, 1938; Stewart, 1941). Polypoid adenomatous and hyperplastic overgrowths of the pyloric stomach occur spontaneously in a special strain of mice, with clinical features similar to those of adenomatosis in man, which also in a few cases has had a hereditary element, but no reliable method has so far been observed of inducing the tumours in animals (Stewart and Andervont, 1938).

Borrmann's (1926) summary of the evidence for each view, with some additions, is as follows. For the congenital origin it is urged that the form and the epithelial tissue, which microscopically is often irregular and atypical, is characteristic of growth, and the undifferentiated cubical cells suggest an embryonic structure; that these polyps occur in the young and occasionally in the newly born; that the familial or hereditary factor is observed in diffuse alimentary polyposis of children, which may involve stomach, duodenum, and colon (Stewart, 1931), and that the commoner gastric variety is indistinguishable anatomically from the intestinal; that evidence of inflammation is often wanting; that there is a clear margin between the normal and abnormal tissues; that gastritis is common and polyps rare; and that inflammation produced experimentally with various irritants, including parasites, has seldom, if ever, produced tumours of this histological character.

In favour of an inflammatory origin, points are that gastritis, though often followed by atrophy, may cause hyperplasia of both connective and epithelial tissues; that in some instances of hyperplastic polypoid processes there may be atypical epithelium with formation of new 'snake-like' glands, and in polyposis (Meulengracht, 1913; Rosenbach and Disqué, 1923) in which most of the membrane may be adenomatous, evidence of preceding gastritis is reported at certain areas, although in other cases, such as those of Stewart (1913) and Mills (1922) such evidence is wanting; that experimental irritation has produced papillomata in animals, though these are usually of squamous epithelium; and that whilst adenomata do occur in infancy, those we see clinically in the stomach are believed to evolve mostly in later life. This last point does not exclude a developmental origin, for other such tumours, such as dermoids, can grow in middle and later life.

Borrmann (1926) believed that gastritis is only seldom the occasion of the growth of an adenoma, and not then of its origin. In the clinical observation of the small series recorded in this paper it is notable that hypertrophic gastritis of the type described in Part II below, in which inflammatory hyperplasia is the main feature, with extensive metaplasia, is as a rule free from the adenomatous polyp. The two views are combined in the conclusion of some authors, such as Ribbert (1904), that certain cells are congenitally disposed to overgrowth and that inflammatory stimuli may be a releasing factor, a suggestion which does something to account for the discrepancy between the frequency of gastritis and the rarity of polyps.

Gastric Polyps and Pernicious Anaemia

Here and there in the literature the combination is recorded of hyperchromic anaemia, anisocytosis and poikilocytosis, smooth or atrophic mucous membrane, achylia, and one or more polyps of the stomach (Moore, 1927; Holmes, 1927; Balfour and Harper, 1933; Pendergrass, 1930). Previous haemorrhages are frequently, but not always (Haring, 1932), reported. In some the anaemia later became hypochromic (Haring; Christoffersen, 1934)

and in some an anaemia which had been diagnosed as pernicious anaemia recovered after removal of the growth (Stephenson, 1927; Allen, 1930). Certain of these polyps were becoming or had become malignant. Such cases have been looked upon as secondary anaemia (Balfour and Harper, 1933) simulating a pernicious type (Moore, 1927; Holmes, 1927; Pendergrass, 1930), and of the same nature as some of the cases of macrocytic anaemia which may occur after gastric resection (Vaughan, 1932; Hurst, 1932; also Case 28, p. 16), stricture of the small intestine and other intestinal lesions, and with *Diphyllobothrium* (Christoffersen, 1934; Whitby and Britton, 1939). In earlier accounts the blood report is sometimes incomplete.

Other cases with polyps are reported as suffering from real pernicious anaemia. In these, neurological symptoms were more frequent and treatment with liver extract was needed after operation (Pancoast, 1927; Haring, 1932; Joyce and Diack, 1933; Conner and Birkeland, 1933; Priestley and Heck, 1935). In the case of Benedict and Allen (1934) the diagnosis had the authority of W. B. Castle.

Surgeon-Commander Ungley, R.N.V.R., has kindly permitted the writer to read an unpublished review in which fresh evidence is brought of a more frequent relation of true pernicious anaemia to polyps of the stomach than has been formerly recorded.

I. POLYPS

Radiological technique. Tumours may be usually, though not always, recognized by studying the gastric furrows or striae with a trickle of barium in them, the rugae or folds being thus displayed. With the larger tumours there is also a filling defect as more of the opaque fluid enters. To obtain a good striate pattern the stomach must be empty. A clean mucosa is especially important in cases of this kind in which mucus is sometimes profuse. The patient takes no food or fluid from 10 p.m. until examination the following morning. If the stomach is partly obstructed, gastric lavage may be used or further examination put off until after a longer fast.

The patient, who has been screened for opacities, reclines on the Potter-Bucky diaphragm and is trained to hold the breath at inspiration and expiration. The advantage of the former is that compression can be made, if need be, on parts otherwise covered by ribs. Compression is used when material is apt to pool, otherwise breathing movements and alterations of posture do what is needed. The opaque medium used is 'Raybar Cream' and water, mixed to such a viscosity that it will coat the crevices on the tongue. Three or four teaspoonfuls are given to the patient, who is lying on his back, and takes a few deep inspirations. He then sits up while still breathing strongly. The posterior wall and the pyloric half have now been coated, and if desired a film is exposed, supine, which will show chiefly the posterior rugae. The patient then turns face downwards, still with forced breathing; an anterior radiogram is made, also a right oblique one, almost lateral; and the left oblique if so desired, but this is of less uniform value

except occasionally for a hook-shaped stomach, and always with gastroenterostomy. A funnel confines radiation to the minimum area which is being inspected, and the exposure as a whole will be the least which is necessary for the weight and build. Five c.c. of fresh peroxide of hydrogen (10 volumes) are sometimes added to a second small drink for the striate pattern. Bubbles from it, seen when screening, may indicate blood, mucus, or other loose organic matter.

Small benign tumours, especially if single, are easily overlooked high up in the cardia, where the pattern may normally be much less regular. In other parts little processes of the mucous membrane such as that shown in Plate 1, Fig. 1, or the small polyp of Plate 1, Fig. 3, may not be detected radiologically; the polyp of Plate 1, Fig. 4, was so recognized. The pattern in the pyloric area is revealed by gentle pressure. In some a better striate pattern may be observed as the stomach empties than at the filling; also barium may adhere to the under surface of a polyp and show itself best at that stage. With adequate preparation and care, errors from flecks of mucus, food residues, and bubbles can be avoided. A mottled picture (Plate 7, Fig. 22), similar to that of polyposis in the intestine, with small punched out or crater-like filling defects, is given by multiple small growths in the stomach. In Case 2, seen 14 years ago, the crinkled contour of the pyloric part (Plate 4, Fig. 9) corresponding to early multiple polyps (Plate 5, Fig. 10) was recognized and it was noted that peristalsis passed along, but did not disturb, the wavy outline. In advanced cases of polyadenoma there are extensive irregular filling defects (Myer, 1913).

With larger tumours also the entry of the barium should be studied as it trickles down the furrows; it may be seen going round the mass. Normal-looking rugae can frequently be traced right up to the tumour unless, as in Case 3 (Plate 4, Fig. 11), there is also gastritis. The filling defect becomes obvious as more opaque matter enters. If the stomach were filled at once with barium smaller tumours would often be missed. The defect usually has a smooth outline, though it may be nodular. The appearance is that of a vacuole enclosed within the curves of the stomach wall (Plate 4, Fig. 11, and Plate 7, Figs. 17 and 22). Greater penetration may bring out vacuoles which would otherwise not be seen. In Case 1 the pedicle also was demonstrated. Compression may be needed. The peristalsis is unimpaired even with large benign tumours and the stomach wall can be seen to be flexible. The remarkable freedom of the gastric muscle was demonstrated in Myer's (1913) case of large masses of polyps; strong peristalsis could be seen, and heard with the stethoscope, and a hardening felt as with foetal movements. In the cardia peristalsis is not obvious, but the natural curve of the stomach wall can still be seen (Plate 7, Fig. 17). Overactive peristalsis will suggest obstruction. A mass with a long pedicle may prolapse into the duodenum, causing a filling defect at the site of attachment. Tumours in the muscle wall, like certain myomata may, of course, block peristalsis. Their smooth outline, with normal rugae, may still suggest benignity.

A tumour may be freely mobile to gentle pressure or change of posture, as in Case 1. Foreign bodies are still more movable. Occasionally a 'crater' appearance is shown on a tumour (Gage, 1937; Davidson, quoted by Christopher, Benjamin, and Sauer, 1941) which proves to be the site of ulceration. Sharp-edged niches are also reported to have been seen by X-rays and confirmed at operation in two cases, which had bled, of neuroma in the stomach (Odqvist, 1937). The rate of emptying of the stomach is usually normal, and may be so even if the polyp is near the pylorus.

The diagnosis from other gastric filling defects can often be made. Cancerous tumours have not the same smooth outline, and peristalsis is interfered with at an early stage. The rugae close to the mass are usually disturbed. With the gastritic oedematous swellings, discussed below, the striate picture is also disordered near by, and peristalsis is not arrested though it may be slowed. Repeated examinations may be needed, for hypertrophic folds viewed in certain aspects can simulate polyps, as in two of our cases, unless continuity with a fold can be traced. In one, repeated examination showed a polyp. In the other, observed twice at an interval of four years, no decision was reached; the patient died of heart disease so that further examination could not be made, and he is not included in the present series.

If the stomach does not dilate fully at the level of a filling defect, gravity is brought to bear to distend that part, the patient being asked whether at any stage of dilatation discomfort is felt. A fixed or nearly fixed approximation of opposite sides is suspicious of malignancy, whilst an unimpaired gastric diameter is strongly in favour of a benign lesion (Plate 4, Fig. 2, also, Case 8, Plate 4, Fig. 18, and Case 28, Plate 7, Fig. 22). The malignant degeneration of a polyp, however, cannot be recognized at an early stage, mainly because of the absence of infiltration of the muscular coat; later the appearance is cancerous. The recognition of the larger polyps is not difficult. Ten of our own 11 cases were diagnosed radiologically and nearly all the recent cases in the other groups reported. In those coming to operation, which would naturally not be early cases, Balfour and Henderson (1927) report that 53 of 58 cases were recognized and that half of them were diagnosed before operation as benign.

Gastroscopy. Illustrations are given of gastric polyps and hypertrophic gastritis seen through the gastroscope (Dr. Pieton Davies, Mr. H. W. Rodgers, Mr. Howell Hughes). Nearly all the present cases were recorded before we were using that instrument. Rodgers (personal communication) writes that he has seen about 12 gastric polypi, usually small, sessile, and hemispherical, rather translucent, more in the body than the antrum, and as a rule not associated with any local inflammatory change. The smaller tumours, like the one shown in Plate 1, Fig. 3, would not often cause symptoms which would bring them into a series such as is here described.

Frequency. The 11 cases of polyps in our small series, including the one duodenal, were found in the X-ray examinations of 4,424 people, that is in 0.25 per cent.; when compared with the number of patients admitted in the

same period, namely 7,684, the frequency was just under 0.15 per cent. A proportion of the cases was not X-rayed for any alimentary symptom, but by request of the doctor as part of investigation.

In statistics of large numbers of autopsies some of the figures from different sources are as follows :

Date	Author	No. of autopsies	No. of benign tumours	Percentage
1912	Tilger (quoted by Chosrojeff)	4,500	14	0.3
1931	Stewart	12,800	56	0.4
1935	Lawrence	7,000	50	0.7
1936	Rigler and Ericksen	6,242	49	0.8
1940	Buckstein	21,026	76	0.4

In Buckstein's (1940) figures from the Bellevue Hospital, New York, 28 benign tumours were also found at operation in the same period.

As regards the incidence of the very rare polyposis, as defined on p. 3, distinguished from a few or several polyps, Borrmann (1926) reported one case in 11,475 autopsies, and four cases were reported by Balfour and Henderson in 1927. In 1919 Balfour had found one in 8,000 operations upon the stomach. Carman (1920) detected two cases in 50,000 X-ray examinations of which one was that reported by Balfour (1919). From the pathological museums of this country we have collected nine cases with a clinical history, one of which has been published (Gage, 1937), and nine other specimens. New cases are published from time to time and we have heard of a few that have not been recorded.

The gastroscopic frequency of benign tumours was found by Schindler (1937) to be 1.5 to 2 per cent. of all cases gastroscoped. This higher figure, as compared with autopsy records, is to be expected, since that instrument is not used without a fairly rigid selection of cases. With a freer use the incidence may be lower. Mr. Howell Hughes saw one polyp (Plate I, Fig. 4) in over 2,000 examinations.

Frequency in relation to cancer of the stomach. In the time under review 102 malignant tumours of the stomach were diagnosed. The proportion of benign tumours to the whole, arrived at radiologically, was therefore just under 10 per cent. This figure compares with those of Rigler and Ericksen (1936), who found 27 tumours, including two duodenal, out of 239, that is 11 per cent.; Lahey and Colcock (1940) give 26 per cent., and Stewart (1931) found that over 15 per cent. of gastric epithelial tumours were benign. Eusterman and Senty (1921) gave the proportion of benign tumours, coming to operation, to all gastric tumours operated upon as 1.3 per cent. Since many benign tumours become malignant and the figures are collected in different ways, they are only broadly comparable.

Frequency in relation to peptic ulcer. During the same period in which polyps were diagnosed in 11 patients there were admitted 570 persons with peptic ulceration. About two cases, therefore, with a gastric or duodenal polyp were detected for every hundred cases of peptic ulcer.

Relative frequency of varieties of tumours. Pathologically the papilloma, adenoma, and so-called fibro-adenoma are classified together, as they belong to

the same group of epithelial tumours, varying in structure according to the type of the epithelial overgrowth and its proportion to the connective tissue. In this whole series, of the cases examined pathologically, there were 51 cases, including one carcinoïd, of epithelial type, 11 myomata, and two lipomata. At operation the relative proportion of myomata was greater, eight of them to 16 epithelial tumours. This accords with the published figures of Judd and Hoerner (1936) and of Rigler and Erickson (1936). Of 76 benign gastric growths found at autopsy (Buckstein, 1940) 60 were 'fibro-epithelial' tumours and 15 myomata, with one lipoma. A preponderance of the first group at autopsy, as compared with operation, seems to suggest that many of the growths which cause no symptoms are of the adenoma or papilloma type.

Site. Any part of the stomach may give rise to a polyp, but they are most often found in the body and prepyloric part. Of 38 cases in this whole series with details of site, in 18 the growths were about the mid-stomach and in 16 near the pylorus. In polyposis the whole stomach may be affected, either sparsely or profusely; of 14 cases in which detail is given, including Case 2, in six the mid-stomach was mostly concerned and in four the prepyloric region. In two the cardiac and pyloric parts were free. Judd and Hoerner (1936) reported a series of 50 various benign tumours encountered at operation, of which 10 per cent. were in the cardia, 24 per cent. mid-gastric, and 56 per cent. near the pylorus. Conway (1936) found four out of 19 leiomyomata on the lesser curve. The four adenomyomata in Stewart and Taylor's (1925) series were all near the pylorus.

Age. We do not, of course, know when a polyp begins. Our patients were mostly middle-aged, the average age being 55 years. In the whole series the age is stated in 57 cases with an average age of the same figure, 55 years. The youngest was 25 (myoma) and the oldest 81 years. The average age in the epithelial tumours alone was 56 years, also for the polyposis cases alone. The myomata occurred, or at least developed symptoms, rather earlier, at an average age of 50 years. In Rosenbach and Disqué's (1923) 122 collected cases 84 per cent. were between 40 and 90 years old. In Balfour and Henderson's (1927) 58 operation cases of various benign tumours the age varied from 8 to 69 years. One of Ménétrier's (1888) subjects with a single polyp was 91 and one of Meulengraet's (1913) 82 years. Conway's (1936) 19 leiomyoma subjects were from 10 to 90 years old.

Sex. Our patients were seven women and four men. In the series, the sex is given in 59 cases, 30 men and 29 women. There were more men with single or a few epithelial tumours and a few more women with myoma; in the polyposis groups the sexes were equal. They were also equal in Conway's (1936) 58 leiomyomata. In Balfour and Henderson's (1927) series of mixed tumours there were 35 men to 23 women.

Number of polyps. Of 69 cases in the series just over half, 37, had single tumours. Others had varying small numbers. There were 19 cases of polyposis, from those having more than a dozen or so to large numbers. This is

the same proportion as that reported by Rosenbach and Disqué (1923) who in 124 collected cases found about half with single polyps; in 19 of their cases the growths were numerous or many.

Case Reports

Case 1. (4522) 1928. A single large adenoma. A rather frail man of 67 years. Former dengue, cholera, and dysentery in the East. Recently nausea for several months and loss of weight. Constant discomfort in the mid-epigastrium and behind the sternum, flatulence, nausea, and giddiness. Physical examination negative. Blood count fair. No free hydrochloric acid in the gastric juice. Occult blood in the faeces. X-ray showed a mobile, pear-shaped filling defect on the greater curvature, the outline above it being somewhat deformed (Plate 4, Fig. 5). The diagnosis of a polyp was made and exploration was agreed upon, as little as possible to be done. The writer was not present at the operation, by Sir Berkeley Moynihan, when five-eighths of the stomach was removed. The patient died six days later. The mass was a large pedunculated polyp springing from the line of the greater curvature and is shown in Plate 5, Fig. 6. The histology of the tumour (Prof. M. J. Stewart), a cellular adenoma which had undergone carcinomatous change, is illustrated in Plate 1, Figs. 7 and 8. The pedicle was mainly free from growth and there was no tumour tissue in the stomach wall.

Case 2. (4516) 1928. Adenomatous polyps associated with carcinoma. A woman of 50 years had complained for two years, with short intermissions, of constant pain in the stomach, worse after food, and of an unpleasant taste. Recent loss of weight. Examination—fairly nourished; slight tenderness epigastrium. Blood count normal. Gastric juice subacid, free hydrochloric acid present. Faeces—no occult blood. X-ray (Plate 4, Fig. 9)—filling defect on lesser curve with arrest of peristalsis there; scalloped outline of greater curve, in pyloric region, shown in serial films to be independent of peristalsis; much gastric delay, though pylorus open. Diagnosis—polyps, growth suspected; exploration advised. Operation (Sir Berkeley Moynihan)—at site of lesion on lesser curve a small lump felt from outside; small lymph nodes on lesser, and one on greater curve; partial gastrectomy. Recovery. The patient is well 14 years later. Pathology (Plate 5, Fig. 10)—a flattened ulcer on lesser curve, about $1 \times \frac{1}{2}$ in., with superficial scirpiginous edges; wall proximal to this thickened; 2 in. away, towards the greater curve, a spherical sessile polyp, the size of a large pea; about the ulcer are numerous small sessile bodies, some rising from the surface, others around more flattened. Histology (Prof. M. J. Stewart)—the ulcer shows the structure of a carcinoma, extending into the muscularis mucosae; the nodules are benign adenomatous mucosal thickenings, with a structure like that in Plate 3, Fig. 24; the mucosa generally shows an advanced atrophic gastritis with an extreme degree of intestinal (acquired) heterotopia.

This appears to be an early case of polyadenoma, with a cancerous ulcer. A part of the stomach was less affected and some free hydrochloric acid was secreted. Both the appearance of the excised part of the stomach, as shown in Plate 5, Fig. 10, and the histology, suggest that it might have become typical polyadenoma had not the cancerous ulcer led to a successful resection. The benign adenomatous mucosal thickenings are characteristic. The atrophic gastritis of the rest of the mucosa with degeneration of the epithelium to an

intestinal type is similar to that observed in places between the polyps in some cases of polyadenoma, though not in others. The association also with a cancer or a cancerous ulcer is recorded in a number of these rare cases and is discussed on p. 27. It appears that such a gross proliferation as that described by Myer (1913) of grape-like masses causing large filling defects, was able to develop because malignant degeneration had not interfered with the progress of the adenomata.

Case 28. (Prof. Davie.) Polyadenoma. A woman aged 53 years. Ten years' history of dyspepsia, frequently coming on when hungry, relieved by alkalis. Appetite good. Haematemesis the day before admission. Test meal—no free hydrochloric acid. X-ray (Dr. A. E. I. Connolly) (Plate 7, Fig. 22)—multiple round filling defects. After treatment for five weeks in hospital a high gastrectomy was done by Mr. Kirk Wilson. Several polyps were also ligated and removed from the remaining part of the fundus. Recovery. Plate 8, Fig. 23, is a photograph of the excised part of the stomach. Plate 3, Fig. 24, is a drawing of the section, showing adenomatous tissue. Three years later macrocytic anaemia, resistant to liver extract, but yielding to ventriculin, occurred.

Case 34. (Prof. D. F. Cappell.) Hyperplastic and adenomatous polyposis. A woman aged 39 years. One year previously teeth extracted for pyorrhoea. Weakness, loss of appetite, and weight for several months. No complaint of gastric disturbance. Tongue painful. Numbness and tingling of hands. Test meal—mucus abundant, no free hydrochloric acid. Haemoglobin 66 per cent., red cells 5,000,000 per c.mm., white cells 11,000 per c.mm. No nucleated red cells. Occult blood in stools. X-ray—many small filling defects in prepyloric part of stomach, presumptive diagnosis of multiple polypoid growths. Operation—partial gastrectomy by Mr. John Anderson. Recovery. Plate 8, Fig. 25, shows the condition of the excised area. There was erosion of the surface of some of the polyps. Histology—elevations of hypertrophic mucosa with a delicate connective tissue core, and abundant inflammatory infiltration with polymorphs, lymphocytes, and plasma cells, superimposed upon an adenomatous element.

Case 35. (Dr. F. G. Hobson.) Polyposis, hyperplastic, proceeding to atrophy. A woman aged 60 years. A brother died of cancer of stomach at 60 years. History (Drs. Dalgleish and Leyton)—former puerperal eclampsia, occasional epileptiform fits since. Otherwise well. Over four years ago began to suffer from distension $\frac{1}{2}$ hour after food and pain to left of navel, relieved by alkali, later vomited frequently. Constipated. X-ray—carcinoma was suspected. Was treated with allyl isothiocyanate and improved. Eighteen months later a second X-ray examination showed small round filling defects all over the stomach (Plate 7, Fig. 26). Had kept fairly well, having no distension or vomiting, but some pain at times, and recently more, with water brash. Appetite good throughout. On 11 March 1942, large haematemesis, 'half a bucketful'. On admission to the Radcliffe Infirmary, weak, pale, motions red with fresh blood and clots. Pulse 80. Blood-pressure 90/50. Haemoglobin 30 per cent. Blood-urea 147 mg. per 100 c.c. Two transfusions were given, and fluid diet gradually increased. Diarrhoea was troublesome. I saw this patient through the kindness of Dr. Hobson, on 28 March. She was pale with a fair amount of subcutaneous fat, not cachectic, comfortable, hungry. She complained of pain to left of navel and a little below. Tongue

clean. Six remaining teeth not good. Eyes clear. No tumour felt or glands. With treatment the haemoglobin improved slowly up to 80 per cent. On re-examination with X-rays the polypoid appearance was no longer present. The gastroscope (Miss Newhouse) showed the mid-stomach purplish, congested, and mamillated (Plate 1, Fig. 27) and the pyloric region atrophic; no polyps.

In three years the progress towards atrophy, apparently complete in the pyloric region, which had previously given the radiological picture of Plate 7, Fig. 26, is striking. The recent haemorrhage presumably came from the congested middle area. The reader who perseveres to the second part of this paper will note that while both kinds of polyposis are considered here together, this hyperplastic variety approaches in its pathology the hypertrophic gastritis there discussed. Indeed Case 62 (Appendix G) is like Case 35 in its course, though the polypoid swellings had not the clear-cut appearance which is classed as polyposis. It is known, and is demonstrated in some of the cases described in Part II, that hypertrophic gastritic swellings can, and do, diminish and disappear. In the consideration of these cases (35 and 62) it cannot be assumed that benign epithelial polypi of the stomach are incapable of regression, since it is well known that squamous papillomata of the skin may disappear spontaneously.

Case 3. (9445) 1940. Leiomyoma. An athletic man of 49 years had lived in the East and had probably had dysentery, because he had been treated with emetine. He had suffered three severe haemorrhages from the bowel in the past five months, in the first one the haemoglobin falling to 18 per cent. and the red cells to 1,000,000 per c.mm. Complications were phlebitis in one leg and a pulmonary infarct. There was no dyspepsia, tenderness, or palpable tumour. With transfusions, rest, diet, and medication, the haemoglobin gradually rose to 72 per cent. The test-meal tube and gastroscope were on purpose avoided. Occult blood was usually present. X-ray showed a large spherical filling defect in the body of the stomach (Plate 4, Fig. 11) with hypertrophic gastritis in the cardiac end. Operation (Sir Robert Kelly) —after a pleuritic effusion, which followed the infarct, had subsided the abdomen was opened (1941), eight months from the first haemorrhage; the stomach presented with a tumour inside; on exposure of the posterior surface in the lesser sac a bulbous swelling, bluish at its blunt apex, projected; the middle part of the stomach, with the tumour, was removed. Recovery. The mass was sessile. The mucous membrane covering it was a little ribbed and of a normal colour, except for an irregular blood-stained area at the pole, where the previous ulceration, partly healed, had caused bleeding (Plate 5, Fig. 12). The tumour was mainly composed of unstriped muscle with a capsule of fibrous tissue lying between it and the mucosa. Most of the mucosa was of fundal type, but in an area of pyloric type the tumour had grown into the mucous membrane at the site of ulceration; here the tumour tissue had assumed a more irregular character and had ceased to form bundles of spindle cells. This was regarded by the pathologist, Prof. M. J. Stewart, as indicative of a low-grade malignancy (leiomyosarcoma). Further evidence of this change was afforded by the presence of mitotic figures and by the ill-formed, thin-walled character of the vessels of the growth. The histology is shown in Plate 1, Figs. 13 to 15. The patient was seen eight months later and was well. He had been taking

vigorous exercise. The gastric juice gave 60 of free hydrochloric acid. There was X-ray evidence of mild gastritis. A year later he also reported well.

A case of Webber and Anderson (1940) is closely similar to this one in the absence of dyspepsia, the history of hæmorrhages, the anaemia treated by transfusions, the X-ray picture, the 'cotton-reel' shaped large tumour projecting on each side of the postero-inferior stomach wall, the histological structure, and the good result of surgical treatment. In the hæmorrhages, the treatment as a duodenal ulcer, with benefit for a time, and the surgical result, the first case of Conway (1936) is similar, but in that patient there was a nine years' history of dyspepsia and the tumour, a smaller one, was not detected by X-rays.

Cases not explored surgically. The following six cases have not, so far, been operated upon. It is important to record them. For in the literature the advice is commonly stressed that all gastric polyps should be removed when discovered on account of the danger of malignancy. In this group no patient in whom it was decided not to operate has died of the disease or developed progressive symptoms, with varying periods from 2 to 12 years since the diagnosis was made.

Case 4. (5573) 1930. A woman of 55 years complained of pain from the breast bone to the throat two hours after food and in the night, relieved by alkali or food, and of eructation of wind. Blood count fair. Gastric juice subacid; free hydrochloric acid 10. No occult blood. X-ray, ulcer not deep, close to pylorus. On the lesser curve above the pylorus a filling defect the size of a hazel-nut. With more barium a little vacuole was seen in the opaque shadow of the antrum. The protuberance at first gave rise to the suspicion of malignancy and operation was discussed. With full ulcer treatment, and rest for the first month, the symptoms almost disappeared. Further X-ray examinations two months and four months after admission confirmed the clinical evidence of healing. The small oval tumour remained the same. At a test meal after treatment the free hydrochloric acid index was 55. Twelve years later the patient is well and leads an active life.

This small definite tumour had presumably nothing to do with the symptoms; or if it had, any irritation of its surface subsided with the treatment for, and the healing of, the ulcer.

Case 5. (5611) 1930. A woman of 41 years was admitted complaining of constipation, nervousness, and sore tongue. She gave a history of an enlarged thyroid gland when younger. There were no digestive symptoms and no occult blood in the stools. The blood count showed hæmoglobin 78 per cent. and red cells 3,400,000 per c.mm. Gastric juice was subacid, free hydrochloric acid present. With X-ray there was a constant single filling defect on the greater curvature at the cardiac end on each film with the appearance of a small polyp. Diagnosis—gastric polyp and a moderate anaemia. The doctor was advised about diet, administration of iron, and use of liver. Re-examination was also advised, but has not been carried out. Eleven years later the patient is known to be well.

Case 6. (8860) 1938. A woman of 65 years complained of arthritis of the fingers and of being tired. No dyspeptic symptom. Occult blood was constant and the blood count was a little below normal. Blood-pressure raised.

X-ray showed a large filling defect in the cardiac end of the stomach, surrounded by barium (Plate 7, Fig. 17), and a duodenal pouch. A consultation was held with an experienced surgeon and it was decided to postpone operation. Over three years later no symptoms have arisen.

Case 7. (9249) April 1940. An able hard-working man of 58 years complained of being tired, of discomfort, belching after food, and distension of the upper abdomen for years; liable to vomit. He had some residual bronchitis after influenza. A round filling defect was observed at the pylorus, not interfering with peristalsis. At times it appeared to enter the duodenum. With correction of diet, 'gastric self-lavage' (described below), paraffin, and rest the symptoms ceased and he put on a stone in weight. Gastroscopy was refused. At a re-examination eight months later the appearance at the pylorus was as before. An X-ray examination is now made at six-monthly intervals. Two years after the first admission he is well.

The mass probably entered the pyloric canal on occasion and caused vomiting, but there is no constant obstruction and when the subject is not over-working, has regular meals, and is careful about strong tea and alcohol, there are no symptoms.

Case 8. (7859) 1935. A woman of 60 years gave a history of melaena three years before. She was admitted for cardiac failure, complicated during treatment by pneumonia. She complained also of heartburn and discomfort after food, sometimes relieved by food; a large polypoid mass was seen near the pylorus. Occult blood was present. With prolonged rest and treatment the heart's action and the general condition improved, though at no time then or since has operation been advisable. After four months from the first X-ray examination the polypoid appearance had increased along the lesser curvature, but three months later there was no further increase. A cautious prognosis was given to the relatives. Since then the patient has kept well with care. It is now $6\frac{1}{2}$ years after the first admission and nine years after the melaena (Plate 4, Fig. 18).

The tumour was at first thought to be a primary malignant growth; later the possibility of an inflammatory mass associated with an ulcer was considered, but on repeated examination the appearance of a polyp was constant and no evidence of ulcer was obtained.

Case 9. (2749) 1928. A woman of 27 years had vomited a large quantity of blood eight months before. She was then treated for ulcer of the stomach, of which, on X-ray, two months after the vomiting, there was no evidence. Two attacks since of nausea, headache, and tenderness in epigastrium, for a few days. On admission complained of headache, epigastric pain half an hour after food, nausea and vomiting, relieved by rest or alkali, with intervals of freedom of a week or more. On examination, no tumour felt, occult blood absent, blood normal. X-ray showed a rounded filling defect in the cardiac end of the stomach with no ulcer crater. The appearances were confirmed by a second examination six weeks later. A diagnosis was made of a single polyp with migrainous symptoms. With rest, diet, bismuth, and cod-liver oil the patient made improvement. That was nearly 14 years ago. Has remained well and is so now.

In each of these six cases, as in Case 8 above, the possibility of some different pathological state, including malignancy and hypertrophic gastritis,

such as is described in Part II, with or without ulcer, was reviewed. They all had, however, the appearance of polyps and of nothing else, and no other diagnosis seems applicable. That conclusion is confirmed by the later history, and, in Cases 4, 7, 8, and 10, by re-examinations. To these is added a seventh case of a patient who has died, but not from the polyp, which was observed with X-rays three times at intervals of some months.

Case 10. (8875) January 1939. A man of 71 years enfeebled by arteriosclerosis, bronchitis, and cystitis, had complained for a year of eructation and hiccup. He was thin. A movable tumour in the epigastrium was suspected on admission. The blood count was fair. No free hydrochloric acid in the gastric juice. No occult blood. X-ray showed a round filling defect in the pyloric antrum. Surgery was not practicable. The patient was under observation from time to time. With diet and medication the symptoms and the nutrition improved. Five months later there was no tenderness or tumour. Eructation continued. Nine months after the first examination he had put on 8½ lb. With X-ray the stomach polyp shadow was the same. The cystitis was troublesome and the specific gravity of the urine fell. During the following winter the general condition deteriorated. Gastric symptoms, except for some flatulence, were not in evidence when he was seen in consultation at his home by Dr. S. W. Patterson, four months before death from cardiovascular degeneration, arteriosclerotic kidneys, and cystitis.

Polyps in the pyloric canal and the duodenum. Whenever the polyp lies near the pylorus, distension, eructation, and vomiting are liable to occur. In Case 7 the filling defect could be seen at times to enter the duodenum. In the following case the tumour arose and lay in the duodenum:

Case 11. (5245) 1929. *Duodenal polyp.* A woman of 67 years had been subject to bilious attacks since girlhood and under treatment at times for the previous 10 years for indigestion. Three years before melaena; duodenal ulcer reported after X-ray. Improved with treatment. The following year melaena twice and again in a Nursing Home for six weeks. On admission complained of a burning in the stomach at 5 to 6 p.m. and sometimes in the night; a different sharp discomfort might occur soon after food and go through to the back. Tip of tongue sore. Well nourished, pale, tender to right of epigastrium. Haemoglobin 44 per cent., red cells 4,200,000 per c.mm., white cells 7,000 per c.mm. No occult blood. Test meal—no free hydrochloric acid. X-ray—pyloric part of the stomach bulged, pylorus and duodenal cap narrow. The narrowness of the cap was ascribed to scarring from the duodenal ulceration which had been previously diagnosed, and treatment on ulcer lines again gave relief. On an attempt to return to full plain diet discomfort recurred, with vomiting. Occult blood was found twice in 12 tests. A second X-ray after five weeks showed the same narrowing. Malignancy was thought to be excluded. With further treatment and light diet the symptoms subsided and the patient left the clinic with no indigestion and rarely flatulence. The blood had improved but little. Eight months later symptoms had returned. Another X-ray examination in Aberdeen showed still a narrow duodenal cap; the second part of the duodenum was dilated. At operation (Mr. Andrew Fowler) a round cauliflower polyp nearly 2 inches long, attached to the posterior wall about an inch distal to the pylorus was present. The growth was reported to be a benign adenomatous polyp. The patient made a good recovery, could eat 'almost anything' and

enjoyed life. Four years later she became pale and died in a few months, aged 73 years, with a diagnosis of carcinoma involving the bile ducts.

A similar case, in which radiologist, physician, and surgeon diagnosed an ulcer at or near the pylorus, is recorded by Reh fuss (1927); a circumscribed fibromyoma was found at the pyloric orifice. Our X-ray examination of the patient was made over 12 years ago. It seems probable that with modern technique, including that of the striate pattern and compression, the tumour would be demonstrated. This was a true duodenal polyp, for the attachment of the pedicle was seen and was distal to the pylorus. It was not one in which, like Case 7 and those of Pendergrass (1930) and Haring (1932), a gastric polyp prolapsed. Fowler, who published the case in 1932, with X-rays and a photograph of the growth, found reference to 25 others. The later supervention of malignant disease throws doubt on the benign nature of the original tumour. Similar recurrences after an interval are recorded (p. 27). Illustrations of duodenal polyps have been published in recent textbooks (Eusterman and Balfour, 1935; Shanks, Kerley, and Twining, 1938; Buckstein, 1940). A stomach polyp may drag the gastric mucous membrane with it, as in a specimen kindly reported by Prof. S. W. Baker of an adenopapilloma impacted in the pyloric ring, traction having invaginated the anterior wall of the stomach. The patient (Case 25) was a man of 58 years who died three days after admission from cardiac failure due to mitral stenosis. No history of gastric symptoms was obtained. Plate 4, Fig. 18, illustrates a case of a polyp passing into the duodenum, relieved by operation, for particulars of which we are indebted to Mr. Charles Wells.

Case 13. A man of 35 years complained of a burning pain in the epigastrium which came on with eating, lasting two hours, or with standing or exercise. It was not relieved by lying down. The severe pain spread from the midline round the ribs to the shoulder blades. There were no periods of remission. Two stones had been lost in five months. He looked ill, epigastrium tender. Test meal—achlorhydria, mucus. X-ray (Dr. J. H. Mather, Plate 4, Fig. 19)—a round filling defect in the duodenum. No delay in the emptying of stomach. At operation a globular mass in the duodenum was reduced into the stomach, where it was attached; it and two other polyps in the stomach were excised. Two tumours were adenomata and the third, in the stomach, had become malignant (Dr. R. H. Mole). After recovery the patient was free from symptoms, the gastric juice was still non-acid. Ten months later free hydrochloric acid was present. At that time the gastroscope (Mr. Howell Hughes) showed some gastritis.

It appears that in this patient either the contraction of the stomach or of the abdominal muscles, or gravity would cause the polyp to move into a position of obstruction. Chosrojeff's (1912) patient also complained of pains on lifting weights. It may be noted that both in this patient and in Case 11, each with a tumour in the duodenum, severe pain going round the right side to the back was felt. In a case observed by Dr. McWhirter (personal communication) the tumour travelled far along the duodenum to the beginning of the jejunum. Plate 7, Fig. 20, is of a film kindly lent by

Prof. Learmonth from the following case of papilloma in both stomach and duodenum. Resection was followed by recovery.

Case 12. A woman of 43 years related that six months before admission vomiting began suddenly, after every solid meal. Weight was lost steadily. Appetite kept up until the last fortnight when the patient became weak and remained mostly in bed. No pain. Suggestion of palpable epigastric mass. Haemoglobin 70 per cent. Occult blood once absent, once strongly positive. Test meal—no free hydrochloric acid, trace of blood. X-ray (Dr. King)—a filling defect in pyloric stomach and in duodenum. Diagnosis—carcinoma of distal stomach. Transfusion was done and a papillomatous tumour found in the stomach and the first part of the duodenum. Resection of those parts. Pathology (Prof. Drennan)—a low-grade malignant papilloma with transmucosal spread to the duodenum where there is a similar tumour. Plate 5, Fig. 21, is a photograph of the excised specimen. The patient left the hospital in two months, and was well 18 months later.

The pylorus and duodenum are not necessarily obstructed, as is shown by the absence of gastric delay in these two and other recorded cases. Meulengracht (1913) found a polyp on a long stalk hanging into the duodenum at the autopsy of a patient who had had 'practically no stomach complaint'. Symptoms may, however, be urgent and severe, as these cases and many records have shown since Collier (1896) reported the case of a man of 21 years who died after an operation for intussusception caused by a polyp near the pylorus, one of many in the stomach, duodenum, and upper jejunum. A patient of La Mouche (1905), a young woman with a six months' history of intermittent vomiting relieved only by abstinence from food, refused operation and died of inanition after four weeks in hospital. An adenomatous pedunculated polyp was found entering the pylorus. With a duodenal polyp, as with those in the stomach, there are cases in which the main sign is haemorrhage. It may be the only one, as in a case reported by Judd and Hoerner (1936) with no dyspepsia. In Case 11 melaena was the chief sign, though there were also symptoms.

Clinical Picture

A study of the cases detailed above teaches that there is no clinical feature which belongs exclusively to any one type of benign tumour of the stomach. Any of the polyps more frequently occurring may (1) be symptomless, (2) interfere with the movements of the stomach, especially at the pylorus, (3) be associated with modification of the gastric secretion, (4) become inflamed or ulcerated with resulting haemorrhage, (5) undergo malignant change. These factors are more important than the pathological structure, for the histology of the growth is the last thing the physician learns about it, and clinical decisions need to be made without that information. The symptoms of all kinds of polyps in the whole series may therefore be considered together under the above headings. Special note is naturally taken of our own cases, and a short section on p. 26 compares the symptoms of the cases of polyposis and of leiomyoma, looked at separately, with the total figures for all cases.

The history of our own cases gave nothing consistent as regards antecedent diseases. Two of the women had had a thyroid affection and two men gave a history of dysentery. In the whole series Case 33 had also had dysentery; otherwise a variety of diseases is mentioned, but hardly any more than once.

Of previous alimentary symptoms, in our own 11 cases three complained of long-standing indigestion; of three others, one had had occasional indigestion, one eructation and vomiting, and one eructation and hiccup. Four had suffered a gross haemorrhage, of whom one gave no history of dyspepsia. In the whole series of 46 cases, including our own, 15 mentioned indigestion for long periods, up to 11 years; 10 measured the length of history by months, three by weeks, and in five there was a sudden onset. In the rest the length of history is not stated. A frequent history is of indeterminate alimentary symptoms for years, or no symptoms, with a recent more or less sudden deterioration from one of the above-mentioned causes. The time of the change for the worse is often clear, as in nine of these cases (1, 3, 7, 9, 10, 12, 42, 43, and 44). This story is similar for different kinds of tumour, both in this series and the literature (Lahey and Colcock, 1940) including neuromata (Odqvist, 1937). Not a few cases, either on account of dyspepsia sometimes relieved by food, or of haemorrhage, have been treated for peptic ulcer, of which X-ray evidence was not found. This was so in Cases 3, 9, 11, 41, and 46, and in many recorded instances.

Symptoms and signs on admission. 1. Small and even large polyps, as mentioned above, may be symptomless, especially if away from the pylorus. This was so in Cases 5 and 6, now observed for 11 and three years respectively; also, after healing of an ulcer in Case 4, a patient who is well 12 years later. The same is probably true of a number of the 24 specimens from museums recorded in the Appendixes, to which no clinical history is attached. Of three of our patients who had no indigestion (one, Case 3, having suffered a haemorrhage) the polyps lay two in the cardiac part and one in the middle part of the stomach.

2. Interference with gastric movements causes dyspepsia, to which alteration of the gastric juice and any inflammatory reaction also contribute. All our four patients with a polyp near the pylorus had epigastric pain or discomfort, one with eructation and hiccup, and one with vomiting. Two of the five with a tumour in the body or cardiac part had pain or discomfort, one with vomiting. Cases 11 and 13, with a polyp in the duodenum, each gave a similar account of an acute pain, spreading round the side into the back. As regards food relation, in six food made the symptoms worse, one with a cardiac polyp, one in mid-stomach, three near the pylorus, and one in the duodenum. Two patients were relieved by food, both with a polyp near the pylorus. Case 2, whose pains were made worse by food, and Case 4, relieved by food, were also the subjects of an ulcer in the stomach. There was usually no tenderness on physical examination. A tumour was suspected on palpation in Cases 6 and 10 only, Case 6 having a large polyp

in the cardiac part (Plate 7, Fig. 17). The growths have been felt in a small proportion of the recorded cases (p. 25).

3. Gastric secretion. A fractional test meal was done on admission in nine cases. In three, all elderly, there was no free hydrochloric acid. Of a further five, two showed superacidity and three subacidity. In a ninth case a test meal was given after a leiomyoma, which had been bleeding, was removed; there was then a free hydrochloric acid index of 60. Miller, Eliason, and Wright (1930) found achlorhydria in eight cases of carcinomatous polyps, also in most published cases. Judd and Hoerner (1936) regard it as constant in benign tumours, Walters (1937) 'quite constant', and Brunn and Pearl (1926) as a feature of 90 per cent. Rehfuess (1927), on the contrary, states that with benign tumours there is usually a normal or high secretion, and Eusterman, and Senty (1921) write that there is no characteristic change in the chemistry of the gastric juice. In a number of published cases, especially those which bled and those found at autopsy, no test has been made; also many collected cases in the papers of different authors are naturally the same ones. I have, therefore, left out collected summaries and taken the cases of authors, 15 in number, reporting on their own patients, and to these added our own and those in Appendixes A, C, and E. A test meal is mentioned 44 times. In 34 there was no free hydrochloric acid, and in 10, six of them leiomyoma (Petersen, 1935; Conway, 1936), free acid was present. In Case 13, from which three adenomata, one malignant, were removed, a little free hydrochloric acid was found a year later. Mucus and fresh blood may be found, as in Case 7. Free hydrochloric acid is, therefore, commonly, but not constantly, absent. It is almost always absent with the epithelial polyps. The matter is of some interest, for, if secretory power be absent it might be expected that polyps are necessarily associated with an extensive atrophic gastritis. The leiomyoma, however, arising beneath the mucosa, need not disturb the secretory glands, at all events of the unaffected areas. Further inquiry is needed in examples of one or a few polyps of smaller size at an earlier stage. It is patients with either large or numerous tumours or those obstructing the pylorus who come to the clinician, and in such, gastric irritation, whether it arose before or after the polyp, is already considerable. The tendency to achlorhydria with advancing age must be remembered. Meulengracht drew attention to this in 1913. In our laboratory it was found by Leigh (personal communication) that in 425 consecutive cases of all kinds the percentage of achlorhydria rose from nine in the thirties to 23 in those over 60 years of age. This figure agrees with that found by Vanzant, Alvarez, Eusterman, Dunn, and Berkson (1932) who reviewed data from 3,746 healthy people; 25 per cent. of those over 60 years were achlorhydic.

No case of Addisonian anaemia, as above mentioned, occurs in the present series; anaemia of 'primary' type has been mentioned above as associated with polyps.

It is not infrequently recorded, in our own cases and in the literature, that the appetite is normal, but six of our 11 patients had lost weight.

4. Most important is the evidence of bleeding—an anaemic aspect, rising pulse, melaena, haematemesis, and the measure of the haemoglobin and red cells. Four of our patients had had a gross haemorrhage, and in two others occult blood in the stools was constant. Two were severely anaemic and four mildly so. In four there was no past or present evidence of bleeding, including Cases 2 and 4, patients who also had gastric ulcer. The myomata, as in Case 3, and the polyadenomata (Cases 28, 32, and 35, Appendix C) are especially liable to bleed, sometimes without warning. Seven out of 12 proved leiomyomata bled, as mentioned on p. 26. Six fatal cases from gastric bleeding were reported by Conway (1936) out of 33 myomata found at autopsy.

5. The liability to malignant change is discussed in a separate section on pp. 26 and 27.

Summary of symptoms and signs from a larger group. For this purpose, as set forth in the Introduction, the 46 cases in the present series with a clinical history are added to 54 published cases from authors recounting the symptoms of their own patients. They are not all reported in the same detail as our cases, but the figures may be regarded as an indication of the main presenting symptoms.

Symptoms mentioned by 100 Patients seeking relief for Gastric Polyps

Gastric pain or discomfort	51	Weakness	17
worse after food	20	Wasting	17
relieved by food	12	Diarrhoea	8
Eruclation	12	Constipation	4
Vomiting	21	Loss of appetite	8
Nausea	12	Tumour palpable	9
Haemorrhage and anaemia	33		

There was, therefore, dyspepsia in half the cases and bleeding in a third. The dyspeptic features, though important, are variable; relation to food is inconstant and loss of appetite is seldom mentioned. The bleeding may be gross and obvious, or 'silent' oozing with a resulting obscure anaemia.

Symptoms in polyposis. Polyposis has, perhaps, on account of its pathological interest, received more attention than its clinical incidence warrants. The following is a short summary of 19 cases, considered separately. Some particulars other than symptoms are included. Of 12 cases of the authors mentioned on p. 6, in those of Cruveilhier (1835) and Ménétrier (1888) there are no clinical details. The other 10, including Meulengracht's (1913) patients, who were under observation in a Home for old people and had no gastric symptoms, may be considered with those of the nine cases in Appendix C.

Symptoms may be severe; it will be noted that there was vomiting in six cases; diarrhoea was prominent in five. In four there was a palpable mass. In four of the patients, two in each group, there was also a cancerous ulcer in the stomach. The cancers were found in adenomatous and not in hyperplastic cases; a separate summary without these cases gave the same relative figures, except that both the deaths after operation were in cases

with such an ulcer. When these figures are compared with those from the 100 cases of all varieties of polyps in the stomach it appears that in polyposis, as would be expected, dyspepsia and haemorrhage were commoner than with one, or a few, polyps. Dyspepsia, in some with a long history, was present in two-thirds of the cases and is probably understated. Polyposis can, however, exist without causing any complaint of indigestion. There was haemorrhage in about half the cases and it was gross in a quarter of them.

A summary of 19 cases of Polyposis

	Ten cases with a clinical history from the authors mentioned on p. 6	Nine unpublished cases from Appendix C	Totals
Gastric pain or distress	7	5	12
worse after food	3	4	7
relieved by food	1	2	3
vomiting	2	4	6
Haemorrhage			
gross	2	3	5
occult	2	2	4
HCl in gastric juice			
absent	6	4	10
present	2	0	2
Detection by X-rays	4	6	10
Operation	5	5	10
Recovery	3*	4	7
Died	1	1	2

* One other case presumably recovered. If that was so the totals are: 10 operations, 8 recoveries, and 2 deaths.

Symptoms of leiomyomata. When Case 3 and the 10 cases of leiomyomata in Appendix E are considered as a group, it appears that these tumours also may cause dyspepsia or be silent for years. Of 58 leiomyomata analysed by Conway (1936), in 27 there was no alimentary symptom. Some in our series, such as Cases 38, 41, and 45, came for relief because of interference with digestion, but often a severe haemorrhage without warning brought the patient into danger. This sequence appears, so far as the present inquiry goes, to be more characteristic of leiomyoma and polyposis, than of the group of single or a few epithelial tumours. Thus in the 12 cases of leiomyoma with a clinical history there was bleeding in seven, which was gross in six. Two died before operation and five were saved by operation, usually with preliminary blood-transfusion.

Cancerous degeneration. The well-known tendency for benign growths of the stomach to become malignant is shown in the epithelial group in Cases 1, 12, 15, 22, 23, and four of the specimens without history, that is, nine polyps in a state of malignant degeneration out of 48 cases. The malignant cells are found first in the periphery, as in Case 1. Stewart (1929) in 263 cases of carcinoma of the stomach thought that about five per cent. were preceded by, and probably arose from, an adenomatous polyp. Miller, Eliason, and Wright (1930) found malignant degeneration in eight out of 23, and Brunn and Pearl (1926) in 12 per cent. of 84 cases. The history in some was long,

10 to 25 years, during which the tumours had presumably remained benign. Balfour and Henderson (1927) report malignancy in only two out of 57 cases. Leiomyomata, which were not included in either of those series, are probably more prone, at least the larger ones, to become malignant, with development of sarcoma. This was so in four out of 12 of the present series, counting the recurrence of Case 37, mentioned below. In Lahey and Colcock's (1940) cases the proportion was higher, namely five out of seven. Malignant growths have arisen in some cases at the site from which a tumour, reported as benign, has been removed. This occurred in Case 11 four years after removal of a papilloma from the duodenum. Recurrence, after a similar interval, is reported by Rigler and Ericksen (1936) and by Balfour and Henderson (1927). The same may occur with leiomyomata, as in the following case, for the account of which the writer is indebted to Sir Robert Kelly.

Case 37. A subserous leiomyoma, outside the stomach, attached to the greater curvature, was removed in August 1927. It was encapsulated and nowhere infiltrating. In May 1931 two recurrent encapsulated leiomyomata were removed, one from each end of the former scar. These projected into the stomach cavity. They were rather more cellular than the first tumour and like it showed some hyaline degeneration. In 1933 malignant growth had recurred with secondary growths in the liver.

Klopp and Crawford (1935) described recurrence of a myoma in the small intestine after 13 years. They suggested that the microscopic diagnosis cannot be relied upon to determine whether a given myoma is malignant or not.

Carcinoma associated with polyps. In Cases 2, 27, and 33 a cancerous ulcer existed side by side with benign polyps. Adding these cases to those of cancerous degeneration of an obvious polyp brings the total, for epithelial tumours, to 12, either cancerous or accompanied by cancer, out of 48. It has been noted many times that benign and malignant lesions are found in the same stomach (Stewart, 1913; Eusterman and Senty, 1922; Mills, 1922; Rigler and Ericksen, 1936). Mills (1922) collected 19 cases of which four were associated with a malignant growth. In some the cancer has clearly arisen in a polyp, but in others a cancerous ulcer is found with polyps not near to it (Rosenbach and Disqué, 1923). Stewart (1913) remarks of such cases that it cannot be shown that the carcinoma developed from a benign growth, but that from its situation that is probable. In the above instances the benign growths were usually adenomata. The association of a leiomyoma with a carcinomatous ulcer was found in a specimen shown to the writer by Prof. Learmonth and Prof. Drennan, Case 46, the dual diagnosis having been made radiologically by Dr. McWhirter. Lawrence (1936) compared his series of 7,000 autopsies with the 11,000 of Stewart (1929) and concluded that whilst about 6 per cent. of polyps became malignant, if cases of associated malignancy in the same stomach are added then malignancy is present in 18 to 28 per cent. of cases with gastric polyps, a proportion which the present series confirms. Varying figures are given by Brunn and Pearl (1926) and authors already mentioned.

Diagnosis

The diagnosis depends upon radiology, described above on p. 10. It cannot be made from the inconstant symptoms and signs. A 'silent' haemorrhage may arouse suspicion, but is more commonly caused by duodenal ulcer without typical symptoms, or by various other lesions. A useful pointer would be the lack of the usual sequence of complaints which is given in commoner causes of gastric disturbance, such as gallstone colic, ulcer, cancer, gastritis, and functional dyspepsia, or achlorhydria with fresh blood and mucus in the gastric juice and without the deterioration of cancer. Weight is lost in some cases of benign growth, especially if the pylorus is involved or there is a more general polyposis. In all unexplained cases, and in anaemias, including those with 'primary' characteristics, the stomach should be examined with barium and, if in doubt, in suitable persons with the gastro-scope.

Excepting a few freak cases in which a piece of polyp has been brought up from the stomach, and possibly some like that of Chosrojeff (1912) who reported that the correct diagnosis was made by the palpation of a soft, mobile, painless tumour in the stomach with anaemia, neither polyps nor polypoid gastritis were recognized until radiology was developed. With X-ray nearly all polyps of any size are shown, and a large proportion of them are diagnosed as benign. Of the others most have been operated upon as possible or probable cancer, the suspicion being relieved later by the pathologist.

In the very rare cases of polyposis involving both stomach and intestines the symptoms are severe haemorrhage, intussusception, or evidence of malignancy, and the patients are young people. An exception, however, is found in Case 18, Appendix A, of sparse small polyps in both stomach and colon of a man of 81 years who died of a stroke.

In our own series 10 out of 11 cases were diagnosed as polyps. Most were observed several years ago, before the regular use of the gastro-scope, which is now passed in patients who are fit for that procedure. If any doubt remains and there is clinical deterioration, operation is advisable as a diagnostic measure, as well as for treatment. There is no means of detecting, either by clinical signs, X-ray, gastro-scope, or direct vision (Lahey and Colcock, 1940) whether malignant change is beginning in a polyp. This can be determined only by histology. The probable nature of the polyp may be surmised from the radiological appearances. Multiple ones and those with long stalks are likely to be adenomata, and a large broad-based one a leiomyoma. This is not a profitable inquiry, for various other forms, mentioned on p. 5, are found from time to time; and whatever the nature of the polyp it may be symptomless, obstruct the pylorus, or bleed; and nearly all forms are liable to become malignant.

Treatment

It will be noted from the foregoing paragraph and earlier pages that many patients in whom gastric polyps have been found after death have lived

through a normal or prolonged span of life with no history of alimentary symptoms. These patients did not come to the clinician, or if they did it was on account of some other illness. Contrasted are the records of patients who have sought relief, usually by surgery; these are advanced or progressive cases. The physician, as polyps are revealed, will seek a mean between these two present sources of information. As time goes on, with modern radiology and the gastroscope, both patients without and those with symptoms are likely to be more accurately observed.

It is clear that when there has been haemorrhage or dyspepsia, weakness and wasting, as in the first three cases, the course is clear; removal is needed, and, if the condition of the patient permits, should not be delayed. Local excision has been practised, but local recurrence is also recorded, and a partial gastrectomy is more likely to give permanent relief. A number of successful cases is reported in the Appendixes. A polyp near the cardia may involve a large operation. In Case 41 Mr. Brock recently removed with success a myoma of the cardiac part which could be seen by X-rays projecting into the air bubble and gullet. Two inches of the oesophagus were excised and the proximal end joined to the resected stomach below. In cases of multiple tumours also removal should be as wide as possible. Lahey and Colcock (1940) recorded a case in which haemorrhage continued and a second operation was needed. The adenomyomata reported by Stewart and Taylor (1925), which caused dyspepsia but not haemorrhage, are not known to become malignant. They are diffuse, the peritoneum appears healthy, and local excision is successful. Recent writers advise excision of all polyps because of the dangers (Judd and Hoerner, 1936; Miller, Eliason, and Wright, 1930). Indeed most published cases are severe, clearly needing surgery.

In quiescent cases the physician must consider three risks, malignancy, haemorrhage, and operation. From figures quoted earlier in the present paper the risk of malignancy, as judged by the huge mass of post-mortem evidence, which includes all stages of polyps, is low. By the clinical evidence it is higher, about 1 in 8 to 1 in 5; and if associated malignancy is taken into account, as it must be, it may rise to 1 in 3 or 1 in 4. The risk of haemorrhage is greatest in polyposis and especially in tumours having the appearance of a leiomyoma. These should be removed whenever possible. Tests for occult blood in the stools will be a guide. As regards the risk of surgery the results of operation upon our own four cases described in the text and those set forth in Appendixes A, C, and E were as follows:

Epithelial tumours (single or a few)	No. of operations	Recovered	Died	Result not stated
Polyposis	10	8	2	0
Myomata	6	5	1	0
	9	7	1	1
	25	20	4	1

It is probable that the case in which the result is not stated also recovered; excluding that, there were 25 operations with 20 recoveries and four deaths; there were also four recurrences.

Balfour and Henderson (1927) in their 57 operations say that all 'uncomplicated benign cases recovered'. Eleven other authors in the literature who give clinical details of their own patients, including the advanced cases urgently needing operation of Miller, Eliason, and Wright (1930), and of Lahey and Colcock (1940), have operated on 30 cases with 24 recoveries and four deaths. In two cases the result is not stated, but from the account they were presumably recoveries. Adding together these figures gives 55 operations with 44 recoveries and eight deaths. The risk of operation, therefore, has hitherto been about 1 in 6 or 1 in 7. With these figures before us it appears that if symptoms caused by a polyp can be allayed by simple treatment, and *a fortiori* if a polyp is an accidental finding and is causing no symptoms, to advise removal is a matter which needs consideration and the balancing of the risk of a gastrectomy, especially in an elderly person, against the risk of harmful developments. As Ribbert (1904) wrote, a lively growth of cells following upon abnormal conditions is not in itself disease; the organism is not ill unless that growth follows certain adverse courses.

In our 11 cases, most of them observed from 4 to 14 years, the only patient who has died from a polyp is Case 1 who was operated upon. Cases 2 and 3 have been saved from fatality by operation and the life of Case 11 was prolonged, with good health, for four years until the age of 73 years. Of the others Case 8 (Plate 4, Fig. 18) would have been operated upon six years ago had the state of the heart allowed, but with improvement in health the symptoms arising from the stomach are less rather than more. Case 6 again (Plate 7, Fig. 17) is a patient who would, in my opinion, be safer with the polyp removed, though the large filling defect is in a less favourable part of the stomach for surgery, namely, the cardiac end. Occult blood was present in the stools, and a mild anaemia though no dyspepsia. On consultation with an experienced surgeon it was agreed to wait; and three years later at the age of 68 years the patient is well and there is still no digestive trouble or gross haemorrhage. In Case 7 the somewhat alarming pyloric symptoms ceased with treatment and so far remain absent. It appears that the mucous covering of a polyp, when irritated, can respond to medical treatment in the same way as the lining of the stomach, of which it is part; and an ulcer upon a polyp can heal, as was seen in Case 3, in which the healed scar of a former bleeding area is visible in the tumour removed at operation. Of the rest, Cases 4, 5, and 9 are well after 14, 12, and 11 years respectively. Case 10 died, aged 72 years, of a different complaint. It is, therefore, clear from the course of these cases that discretion must be used, taking into account the general state and age of the patient. It is not necessary to perform laparotomy upon every patient in whom a filling defect characteristic of a polyp is revealed, unless there is clinical or gastroscopic evidence of distress, progress, or haemorrhage. This applies especially to smaller polyps. Larger ones have clearly grown and if they can be removed with reasonable safety that should be done.

Cases of polyposis need the same careful consideration. Cases 2, 28, and

34 have been successfully operated upon, and others tabulated on p. 26. Case 35, after a profuse haemorrhage, and Case 62, appear to be recovering satisfactorily with regression of the tumours formerly demonstrated. In every case not operated upon, the patient and the family doctor are advised that regular observations must be made from time to time. We agree with Rigler and Ericksen (1936) who refer to patients observed over a series of years, particularly those with single lesions, without any change in the appearance of the tumour, and remark that it is at times difficult to recommend to such a patient so serious an operation as a gastric resection. The medical treatment varies with the symptoms, and the state of the gastric juice and blood. It is mentioned in the cases above related and is similar to that of the polypoid gastritis described in more detail below. Regulated exercise and rest, and simple food with restriction of or abstinence from alcohol and tobacco are important, as in all gastric disorders.

Results

The ultimate result in the majority of recorded cases after operation is not related. Fourteen patients, seven in our whole series and seven from the literature, are known to have remained well for some time. In six others recurrence is recorded. The recognition of polyps except at operation or autopsy is comparatively recent and enough time has not elapsed to assess results on a large scale. The later history of all our 11 cases has been given. Case 1 died after an operation, Case 11 from recurrence at 73 years, four years after removal of the polyp, and Case 10, aged 72 years, of other causes. The remaining eight are alive, two after partial gastrectomy, 14 and $1\frac{1}{2}$ years ago. The six other cases were observed 14, 14, 12, $6\frac{1}{2}$, $3\frac{1}{2}$, and 2 years ago and are known to be well, having been treated medically and advised upon a régime to be followed at home, with re-examination at intervals. In Case 28, a macrocytic anaemia amenable to treatment developed after gastrectomy.

Prognosis

With single or a few benign growths, if recognized, treated surgically or medically, as may be advised, and watched, the outlook is usually good. If malignant degeneration has begun the prognosis may also be good after wide removal. With excision of the polyp and the mucous membrane of its base recurrence is more likely than with a partial or extensive gastrectomy, but in elderly or feeble people the milder measure may carry a smaller total risk. With polyadenoma and myomata the risk of haemorrhage and malignancy is greater. If all the cases, single and multiple, in the literature are taken into account, the majority have died from other causes.

II. POLYPOID GASTRITIS

These massive shadows, which when first seen are alarming, were observed in 19 cases in the years under review, 14 men and five women. These are Cases 47 to 65, tabulated in Appendix G.

The pathology is that of a hyperplastic chronic gastritis, discussed above on pp. 6 to 8. In irritative gastritis, acute or chronic, whether from mechanical or chemical trauma to the surface, or in the haematogenous forms of acute infections, hyperaemia and oedema are prominent (Faber, 1935). Oedematous swelling of the gastric and jejunal mucosae around a gastrojejunal stoma may be very striking in operation specimens. In the cases here discussed the hypertrophy of the mucosa and submucosa with oedema may lead to a thickness of an inch or more. Ménétrier (1888) mentioned a depth of 2 to 3 cm. from the furrows to the top of the ridges. In the case shown in Plate 2, Fig. 29, at a stage of much improvement some of the processes are 2 cm. deep, even after fixation. It is not known why this development should occur in one stomach and not in so many others subject to similar stresses.

In examining material, whether macroscopically or microscopically, it must be remembered that when the circulation has ceased there is shrinkage, and in post-mortem material there is also injury from digestion, unless the stomach has been examined, or injected, without delay. For fixing, five per cent. formalin should be made up with normal saline to lessen the extraction of fluid from the tissue.

These processes are not neoplastic. Versé (1909) described an adenoma growing upon a hypertrophic gastritic fold (p. 7) and becoming malignant; and in the last specimen tabulated in Appendix B (670¹) a few small, dark, warty papillomata (Plate 1, Fig. 46) are growing upon hypertrophic folds. But the sequence or combination of hypertrophic gastritis and neoplasm is not observed by other workers, apart from irritation about the base of a tumour, and may be coincidental. Schindler (1937) writes that there is no acceptable evidence that hypertrophic gastritis ever leads to the development of tumours. On the contrary, a massive hypertrophic gastritis without complications may gradually disappear with treatment, both clinically and radiologically. The change in the mucous lining is presumably towards atrophy, a conclusion which in some of our cases has been supported by the secretory changes after years and, as in Case 62, by gastroscopic examination of the flat non-rugous lining of the stomach, but that is not always the case, for persistent polypoid masses and tags may remain.

We have seen above that some of the cases hitherto described as polyposis are of polypoid hypertrophic gastritis. Such conditions may seriously affect health, as shown by cases 35 and 62, and by that of Hurst and Stokes (1926), but probably carry less risk of malignancy than polyadenoma. It has, however, already been noted that earlier writers (Borrmann, 1926; Stämmeler, 1924; Konjetzny, 1930) describe all stages between gastritic swellings and true adenomata, a matter of pathological interest and importance which is still under discussion.

Radiology of hypertrophic gastritis. The technique is the same as that described on pp. 10 to 12, except that a different scheme is followed to observe a gastro-enterostomy or partial gastrectomy, the drink being given in

a feeder cup during compression of the anastomosis, with the subject face downwards. The actual filling is often radiographed, as a right oblique prone position at this phase has the advantage of showing any extrusion of the stomach through or by the side of the diaphragmatic hiatus, these herniae being intermittent during formation. The oedematous swellings of the massive hypertrophic gastritis here considered are revealed, unless the secretion of mucus is too profuse, as the barium mixture flows round irregular humps or folds, with an appearance of holes of varying sizes and shapes in the opaque fluid. Large bulbous folds may be seen in profile, and rigid filling defects. Peristalsis may be laboured in the affected parts, especially in the lower end of the stomach, but gross swellings occur mostly in the proximal stomach, where waves are more scarce. An area of hyperplasia may be covered with ribbons, or a sheet, of mucus, and the first suggestion may be one of outside pressure. A stomach which cannot be coated with barium, partly or as a whole, should be regarded with suspicion (Plate 6, Fig. 43, in which the outlines are confused by a mass of mucus, between the two arrows, which may be compared with the condition after treatment shown in Plate 6, Fig. 44). With respiratory excursion, changes of posture, and patience, enough barium sulphate will enter the covered furrows to make the true state visible, provided the part is brought into profile, which may entail oblique and lateral views. Gastritis is not revealed when looked at through a thick layer of opaque fluid. In some the striate picture can be seen better at a later stage of filling, or at the emptying stage. It may not be possible to demonstrate the rugosity of the entire stomach on one film; several films may be needed in different postures. A large fold of mucous membrane is not in itself evidence of gastritis, especially on the greater curve, and the optical section of radiating folds at a filling stage on the edge of the cardiac part may be normal. Large folds on the lesser curve, as in Plate 4, Fig. 2 and Plate 6, Fig. 42, are usually abnormal. The chief difficulty in the radiology of the mucosal pattern is to decide between normal wavy folds and early hypertrophic changes, particularly when localized (Plate 6, Fig. 28 and Plate 2, Fig. 29). In this patient the proximal folds approached normal, whilst the distal ones were stiff and hypertrophic. Variations in the contraction of the muscularis mucosae are to be borne in mind, with corresponding degrees of corrugation. Failures must be expected even when trying one's very best, and when in doubt reliance on minor differences should not be encouraged. In hypertrophic gastritis the rugae do not vanish with distension, but they do in a healthy stomach; the diagnosis must not therefore be made on the filling stage alone. The peritoneal outline can often be demonstrated on a film and from it the width of the whole stomach estimated, as well as the thickness of its wall. In case of doubt the diagnosis must be confirmed by repeated examinations or by the gastro-scope. Evidence of rigidity in the folds is looked for in the area affected, with the peritoneal outline as a secondary guide. Normal rugae are not usually more than 1 cm. high, but there are exceptions. It will be

remembered that gastric shadows are magnified on the film. Congenital giant folds are described. Presumably they would not be associated with clinical symptoms and secretory changes as in these patients. Temporary swellings (Berridge, 1942) are excluded by adequate and repeated X-ray or gastroscopic examinations.

It has sometimes been said that the gastroscope does not confirm the radiological diagnosis of hypertrophic gastritis, but that is not our experience. Account must be taken of the attributes and limitations of each method. The difficulties and pitfalls in radiology are here mentioned, and the small number of cases in the present series is evidence of caution in diagnosis, which must be correlated with the clinical evidence. We have to remember that through the gastroscope we see only the surface. The German term *Kamm* (= 'comb' or 'crest') for the swollen rugae implies their depth, which is not shown by the gastroscope, and not always, owing to mucus, fully revealed by X-ray. In Plate 1, Figs. 39, 40, and 41, for example, the observer is looking at the top only of swollen ridges. Between them, under the visible mucus, are valleys and at the bottom of the valleys around the bases of the ridges are spaces of which the gastroscope gives no indication, but which are shown in Plate 5, Fig. 38, a radiogram from the same patient as Plate 1, Fig. 39, also in Plate 6, Figs. 42 and 43. These deep spaces between hypertrophic cushions are liable, when filled with barium, to be mistaken for ulcers (Berg, 1930). It is the large folds, as shown in Plate 1, Fig. 39, seen with X-rays end-on or sideways which cast on the screen or film the images, a little magnified, of bulbous rounded filling defects. From an X-ray point of view, therefore, the term polypoid is justifiable for these appearances, though gastroscopically sometimes it is not. Unlike those of real polyps the shadows are not rounded from all aspects. The flaccid folds of a milder gastritis may show with X-rays, but when the stomach is distended with air they are flattened out or lie down and may be hardly distinguished with the gastroscope. An atrophied mucosa can also be recognized even when local, but this is more difficult, and negative or doubtful observations should be regarded with reserve. It may itself, at the terminal phase of ingestion, show a slightly granular surface.

Case Reports

Hypertrophic gastritis with preceding ulcer or operation. A familiar form of hypertrophic gastritis, often accompanied by great oedema, is that which may be associated with peptic ulceration, especially around unsuccessful or partially successful gastro-enterostomies. There are, in the present series, seven such cases with massive filling defects, five in men and two in women (Appendix G, Cases 47 to 53), and a good many others could be found with inflammatory processes almost as obvious. The average age of these seven patients was 46 years. Four had recent peptic ulcers, of whom one had had a former short-circuit undone, and three had a present gastro-enterostomy. The length of history varied from one to 24 years and the familiar symptoms

of discomfort after food, eructation, nausea, and poor nutrition were related. On examination a variety of conditions was revealed, all the cases, however, showing with X-rays massive filling defects near to the lesion, in four about the cardia and mid-stomach, and in three towards the pylorus. These folds are seen regularly by gastroscopists in such cases (Hughes, 1938). Mr. Harold Rodgers (personal communication) writes of the oedema in a gastric fold on the margin of an ulcer, or at an anastomotic line, which may produce a bulbous appearance which looks like a polyp (see Plate 1, Fig. 40).

Case 52. In a woman (7722) aged 46 years, the subject of a duodenal ulcer with superacidity, the mass looked like a group of polyps around the pylorus. Operation was not accepted and she did well for a time with medical measures. Two and a half years later stenosis developed. The surgeon found adherent to the pancreas a nodular mass which was not removable and was regarded as malignant. A short-circuit was made between the stomach and jejunum for immediate relief. The patient has remained well for over three years.

I have seen palpable tumours around the pylorus and duodenum, believed to be malignant growth, subside after gastro-enterostomy; in a large one a piece was taken out at operation and proved to be inflammatory, in another X-ray showed a perforated ulcer round which a mass had formed (Ferguson and Watson, 1922).

A common feature in this group was the presence of free hydrochloric acid in the gastric juice, in three, all cases of duodenal ulcer, in excess, in two, in very small amount. It appears that in some a considerable inflammatory swelling can occur near to an organic lesion without loss of secretory power, the cardiac mucosa, or a great part of it, retaining its differentiated cellular structure, whereas in others secretory power is lost with histological degeneration of the glands. The two following cases, one of each type, are illustrated by the X-rays and by microscopic sections. In the first the history is given of a young man who was treated at three clinics and whom I saw at intervals over 18 years, the last time two years before his death. It is to be noted that a degree of clinical recovery, at times apparently complete, with increase of weight and vigour, had occurred repeatedly.

Case 47. Chronic gastritis following gastro-enterostomy, with persistent superacidity. A man of 26 years (1704), admitted 1921, gave a history of pain after food at the age of 9 years. At 15 years appendicectomy. Nine years later pains recurred and duodenal ulcer was diagnosed, for which gastro-enterostomy was done. Four months later pains began in the left side of the abdomen. On X-ray examination massive gastritis was evident around an ulcerated stoma. Gastric juice superacid. Improved and returned home to active, anxious, business life. Later haematemesis, and at an operation elsewhere (aged 31 years) jejunal ulcer exposed and the gastro-enterostomy undone, as the duodenum was then thought to be normal. Was reasonably well for a time and weight increased. At 33 years pains recurred and for the next 10 years he was treated at intervals for duodenal ulceration, worse the last year. Medical treatment was hampered by easy induction of alkalosis. On re-admission, aged 43 years, recurrent duodenal

ulcer found. Superacid gastric juice. The gastritis observed 17 years before was still evident at the site of the former stoma, and the piece of small intestine which had been engaged in the anastomosis could be seen enlarged. Medical treatment led to improvement, but not recovery. A partial gastrectomy led to apparent complete health. Gastric juice still superacid.

Plate 6, Fig. 28, shows the persistent gastritis at the former site of the stoma. The mucosa and submucosa at the site of the opacities were of the thickness of a finger. Plate 2, Fig. 29, shows a section of the tissue. On the cardiac side oxyntic cells were abundant. Twenty years of local gastritis and recurrent ulceration had not been accompanied by much metaplasia or loss of acid-producing power. If such change had occurred perhaps the clinical course would have been more favourable. The patient returned, much too early, against advice of physician and surgeon, to a very active life, and cigarettes. With absence of symptoms he was cheerful and confident. In the remaining two years of his life he suffered two perforations. At one of the operations it was reported that an inflammatory tumour the size of a fist was found. He died near his home after an operation for gastrocolic fistula, which involved making three anastomoses. A similar case with duodenal ulcer has been described by Heeks and Gibb (1942).

In the second case, though symptoms had been allayed, gastric function and nutrition had for some years been below normal.

Case 50. Chronic gastritis, following gastro-enterostomy, developing achlorhydria. Admitted 1938. A man of 62 years complained of nausea, sense of fullness, stomach-ache, and eructation with mucus. Some food relief. Delicate childhood, athletic in youth. Gastro-enterostomy 21 years before for duodenal ulcer, after which a good period, though at times indigestion. Nine years before haemorrhage from jejunal ulcer; was treated, teeth removed, and remained well for five years. Symptoms since at intervals. Lived carefully but continual hard intellectual worker, with great responsibilities. Two years before an alcohol test meal gave acidity 14 with index 6 of free hydrochloric acid, much mucus, traces of blood. With X-rays the cardiac part of stomach was contracted and irregular in outline, large folds; a niche on lesser curve; stoma working freely; duodenal cap not seen. On examination, thin, low blood-pressure. Haemoglobin 80 per cent., red cells 4,900,000 per c.mm., white cells 10,300 per c.mm. Abdomen flaccid, not tender. X-ray—gross hypertrophic gastritis of cardiac part (Plate 7, Fig. 30); rapid emptying; stoma appears normal. Diagnosis—gross polypoid gastritis after gastro-enterostomy. Treated by light varied diet, separating fluids and solids, mild gradual exercise, medication, including iron pills, gastric 'self-lavage' with sodium bicarbonate or normal saline solution. Gradual improvement followed and in two months discomfort had ceased, walks were enjoyed and weight had increased by 6 lb. With X-ray the swellings in the stomach were smaller and the wall in that region was less rigid.

The patient returned to onerous duties and with great care carried on with work. Seventeen months later he died after a cerebral thrombosis. *Post mortem* a more massive polypoid mucosa was revealed than an experienced pathologist had previously seen. Between the projections were bridges of mucous membrane over former ulcerated areas. Sections showed, under

the microscope, inflamed hypertrophic mucosa lying over the fibrotic granulation tissue of ulcer bases. The slides, for which I am indebted to Professor Meakins and Professor Duff of Montreal, illustrate gross oedematous hypertrophy, gastritis, and atrophy of glands (Plate 3, Fig. 31), mucosal proliferation at the edge of an ulcer base (Plate 3, Fig. 32), severe chronic inflammation and hyperaemia (Plate 3, Fig. 33), glandular proliferation in places (Plate 2, Fig. 34), replacement of normal gland tissue by a vegetative mucosa (Plate 2, Fig. 35), and metaplasia to an intestinal type of epithelium, secreting much mucus. The case is of clinical interest in that a patient with so severe a gastric lesion was, by a considered régime, relieved of symptoms and was able, with control of diet and rests, to resume for a time a life of usefulness. On comparison of these two cases, 47 and 50, it is seen that the retention of a normal mucous membrane, whilst an undoubted advantage with moderate acidity, as in Cases 48 and 49 (Appendix G) which recovered, was not so in Case 47, with superacidity; for in spite of intervals of health and vigour, catastrophe after catastrophe led to death at 45 years. Whereas in Case 50 the mucous membrane degenerated but was not perforated, the subject, though restricted as regards diet and violent exercise, lived a most efficient life and did work of outstanding value and amount until the age of 63 years when he died of a different complaint. His case leads to the next series, Cases 54 to 65, nearly all with achlorhydria and presumably degenerated mucous membrane, none of which has died of the gastric disease.

Hypertrophic bulbous gastritis without preceding ulcer or operation. This form of gastritis has received but little attention in the literature. Those cases of Ménétrier (1888), in which he speaks of diffuse hypertrophy looking like convolutions of the brain, probably belong to the group, judging from both the written account and the histology. Of recent writings the descriptions of Berg (1930), Kantor (1936), and Buckstein (1940) agree with our experience. We distinguish radiologically 'hypertrophic' cases in which there is a greater degree of the palisade appearance often seen along the greater curvature, as in Cases 54, Plate 6, Figs. 43 and 44 (described below) and Cases 55 and 56. Also 'bulbous' cases in which rounded masses of oedematous tissue occur at other parts of the stomach, as in the other nine patients (Plate 5, Fig. 38 and Plate 6, Fig. 42). Small polyps may also occur which are hyperplastic in structure and not adenomatous, as described on p. 7.

Frequency. Gastritic swellings of this degree, without ulcer or known trauma, are rare, about as rare in the present series as true gastric polyps. The 12 cases are tabulated in Appendix G, Cases 54 to 65. They correspond, as indicated above, to a period of time during which a clinical diagnosis of gastritis was made in 470 patients. The study of the group is of interest. It differs from the last group of gastritis about peptic ulcers, with superacidity, in respects which seem to be characteristic, namely in the situation of the swellings and the chemistry of the gastric juice. The group differs also in the histology which is similar to that of Case 50, described on the previous page, Case 66, Appendix H, and the published sections of Buckstein (1940)

and Faber (1935). There are nine men and three women, the average age being 52 years.

Site. The mucosal proliferation was in seven cardiac, in two in the mid-stomach, and in three general. In no case in this group were the swellings in the pyloric part alone.

Causes. In three patients alcohol was an apparent or even obvious cause; in the other nine it could be excluded.

The X-ray picture of these cases was similar to those already shown. The post-mortem appearance of the stomach of an alcoholic is shown in Plate 8, Fig. 36 (Case 66). Swallowed septic material appeared to be a clear factor in the following case.

Case 61. A man of 44 years (8219), admitted 1936, had suffered for over 20 years, after an injury to the frontal region, in spite of intranasal operations, from recurrent sinusitis. Gastric discomfort was relieved by food but appetite was poor. He was weary and subject to migraine. Free hydrochloric acid 5, with mucus and epithelial cells. X-rays showed polypoid gastritis on the lesser curve just below the entrance of the gullet. Symptoms were relieved, but surgical consultation advised. Much further benefit followed a radical external operation on the diseased frontal sinus.

In two patients, Cases 49 and 58, septic teeth were a probable cause. Plate 8, Fig. 37 (Case 67) shows the state of the stomach of a lunatic who had swallowed rubbish. Its condition may be regarded as mainly the result of ingested sepsis.

In the remaining patients in this group, diseases which may have predisposed were dysentery, thrombosis of leg veins, diverticulosis of the large bowel, syphilis, and diabetes. The occupation, that of a cook, was a possible factor in one patient.

In the following case the X-ray film and the gastroscope drawing may be compared.

Case 57. Polypoid gastritis with colitis; seven years later growth of colon. A thin man of 48 years (7298), admitted 1934, overactive at work and play. Liable to looseness of the bowels when fatigued or after dietary indiscretions, with stomach feeling upset and occasional vomiting. Never able to eat a heavy meal, pastry, crab, onions, and other 'less digestible' foods. Two glasses of wine daily and formerly about 20 cigarettes, but had for three months ceased to smoke. Complete dentures. No tenderness or tumour. Blood-pressure 130/100. Haemoglobin 93 per cent., red cells 4,800,000 per c.mm. Free hydrochloric acid highest 20, excess of epithelial cells. X-ray—massive folds in cardiac region (Plate 5, Fig. 38) which persisted with filling; irregular haustration of colon. Diagnosis—overtired, with recurrent colitis and hypertrophic gastritis. Treatment—regulated rest and exercise, a plain diet with sieved greens and baked apple each once a day. Gastric 'self-lavage' twice a day, an hour before chief meals. Medication included kaolin, bromide, and bismuth. In six weeks he was rested, had gained 3½ lb., and could walk with pleasure. Advised to follow regular régime. On readmission four years later had kept better, but had lost 12 lb. In last few months four of the old attacks with discomfort in right side of abdomen and vomiting of white mucus. No abnormal signs. No tumour felt. Test

meal—muco-pus; now no free acid (histamine). X-ray—anterior surface and greater curvature, large folds, less than four years ago; some contraction of ascending colon and hepatic flexures. Gastroscopy (Dr. Picton Davies)—on anterior surface large smooth folds, not injected, paler than normal, with deep valleys between containing mucus; these opened out but little with distension. Hydrochloric acid was taken and other measures resumed and the patient carried on well. Further X-ray was advised in two months. Seven months later an adenocarcinoma of the ascending colon was removed (Mr. B. R. Sworn) by resection. Good recovery. Patient well nine months after.

The gastroscopic examination illustrated in Plate 1, Fig. 39, was made when the gastritis was less than formerly. It shows the state of the swollen mucous membrane when distended by the air necessary in using the gastroscope. It is easy to understand what bulbous filling defects can be formed when there is little air in the stomach and such folds are bent one upon another. The gastroscopic appearance may be compared with that of Case 60.

Case 60. Polypoid gastritis simulating duodenal ulcer. An active outdoor man of 48 years (7639), admitted 1935, complained of a burning pain in the pit of the stomach and waterbrash. He related that his grandmother and six of her eight children had peculiar stomachs, with burning pain relieved by medicine and rest. Two of these sufferers are now 81 and 85 years. The patient's indigestion began five years before, after three years of hard work, with a burning pain, sour taste, and headache. X-ray reported negative. Symptoms ceased with diet and medicine. Two years before recurrent duodenal ulcer suspected, improved. Six months before, again occurred, would come on about 2 p.m. and was better after tea. Symptoms ceased on a vegetable and fruit treatment, but in a fortnight returned. No alcohol for two years. Eight cigarettes a day. Examination—complete dentures; no abnormal physical signs. Test meal—free hydrochloric acid rose to 55. X-ray—polypoid folds in body of stomach; duodenal cap filled normally. Treatment—rest at first; gastric 'self-lavage'; diet as for later stages of peptic ulcer. The symptoms ceased shortly after admission. Readmitted five years later. He had kept for 18 months to régime advised, with complete relief and returned to it if symptoms appeared. Very little alcohol; 12 to 16 cigarettes daily. Not so well the last year with war duties and anxieties. Tongue showed moist fur, otherwise physical examination negative. Haemoglobin 88 per cent., red cells 4,700,000 per c.mm. Test meal—free hydrochloric acid to 10, much epithelium. X-ray—still polypoid mucosa, though much less than five years before, now approaching the normal. Gastroscopy (Dr. Picton Davies)—free mobility of stomach walls; mucosal folds pronounced on greater curve, injected, somewhat high colour, not obliterated on dilation; no excess of mucus. With treatment symptoms again ceased. The gastroscopic picture (Plate 1, Fig. 41), as compared with Plate 1, Fig. 39, shows more nearly normal folds, though rather more active irritation.

The following is an example of polypoid gastric mucosa in a diabetic with cessation of alimentary symptoms under treatment.

Case 58. A man of 59 years (6479) had been treated in the clinic for diabetes and infected teeth and pyorrhoea, with loss of weight. Diet and insulin were prescribed, and readjusted two months later. After five years:

which he had kept well under the care of his doctor, the patient returned for review. The sugar in the urine and blood had increased, and he complained of loose stools. A fractional test meal gave no free hydrochloric acid (with histamine) and many pus cells. X-ray showed massive hypertrophic changes of the mucosa on the greater curve and the anterior wall of the stomach (Plate 6, Fig. 42). The diabetes was readjusted, and a diet on ulcer lines, with gastric 'self-lavage' prescribed. Re-examination was advised after a short interval. The patient, however, continued to improve on the régime advised and did not return. Four years later his doctor reports that he is keeping well, has no abdominal symptoms, and is active with local war work and in his garden.

Symptoms and Signs

All 12 patients complained of some symptoms referable to the stomach, mentioned in the following frequency—epigastric pain or discomfort 7, eructation 7, nausea 5, vomiting, weakness, and headache 4, loss of appetite and wasting 3, diarrhoea and constipation 3 of each. The food relation of pain had no constancy, thus three were relieved by food and two made worse.

Anæmia was not a prominent feature. It was severe in two patients, one of whom had suffered a gross hæmorrhage. Three others were moderately anæmic; the remaining seven were not so. Indeed in two of the alcoholics, as I have sometimes observed in others, the blood counts were high. Hæmorrhage can occur in hypertrophic gastritis without the assumption of a peptic ulcer. With the gastroscope superficial ulcerations are sometimes seen and a more chronic ulceration can occur. Two such cases are described by Buckstein (1940) and one of them is illustrated. These gastritic ulcers are generally away from the usual site of peptic ulcers and may lie on the greater curvature. In others an ulcer has been demonstrated, e.g. Case 54, cf. also Case 35. Both these patients suffered gross hæmorrhage which hardly seems to be explained by oozing from vascular tissues. Further pathological material is needed. A feature in contrast to the 'ulcer or operation' group is that in 10 of the 11 patients from whom gastric juice was obtained free hydrochloric acid was absent (6 cases), almost absent (1 case), or low (3 cases). Further, in three patients who gave at first a more normal figure, the acidity when observed through the years had vanished, or nearly so. Two of these cases have been described. The following is the story of the third case.

Case 55. Secretory deterioration with clinical improvement. A woman of 64 years (5496), admitted 1930, was the subject of some enlargement of the thyroid, a duodenal pouch, and diverticulosis of the sigmoid. She had noticed a sensation of difficulty in swallowing, with eructation, and her doctor had suspected cardiospasm. A large area of nodular mucosal folds was seen on the postero-lateral surface of the stomach. Test meal—free hydrochloric acid 22, and much mucus. With treatment improvement was shown and six months later the folds were less. Five years later re-admitted; had kept well until a few months before when symptoms of a mild diverticulitis of the colon had developed. No return of stomach discomforts. The gastritic folds had further diminished. The gastric juice now gave no

free hydrochloric acid, much mucus, and some pus cells. The patient responded to treatment for the lower bowel and remained in good health until nearly 10 years from her first admission. She died, aged 74 years, two months after an operation for cancer of the ascending colon.

The three examples of progress towards achlorhydria may be set forth thus:

Cases	Index of free HCl on first admission		Free HCl
55	22	After 5 years	0
57	20	" 6 "	0
60	55	" 5 "	10

This change in the gastric acidity was, in each of the cases, taking place at the same time as clinical improvement. It will be borne in mind that one in four persons above 60 years of age is reported to be achlorhydric, but that does not account for the absent, or low acid in 10 out of 11 persons from age 37 to 64, with an average age for the 10 of 54 years. The changes in the mucous lining explain the deterioration in the secretion. The opposite change is seen from time to time in milder cases of chronic gastritis, as was shown in one of these patients (Case 64), a young man intermittently alcoholic who responded to abstinence and advice, the index of hydrochloric acid rising in two years from 30 and 27 to 85. With loss of free hydrochloric acid mucus is often observed in excess, though in some all secretion may be deficient; in five patients pus was noted and in eight a profusion of epithelial cells and debris.

Diagnosis

The diagnosis from malignant growth is the most important matter. Some of the masses look like carcinoma. Three of the 12 cases with no preceding ulcer or operation had been suspected of malignancy. The absence of the clinical features of cancer with such considerable filling defects is helpful, but a low gastric acidity is equally in favour of the more serious diagnosis. No tumour is usually to be felt. Radiologically the flexibility and power of dilatation and contraction of the stomach are characteristic. Thus the X-ray of a patient with a gastro-enterostomy resembled Plate 4, Fig. 2 (upper section), but the margin of the wall did not dilate, move with peristalsis, or contract as the stomach emptied, a tumour could be felt, occult blood was constant, and the patient was wasting. A diagnosis of rapidly growing carcinoma was made, and was confirmed by the clinical progress. When a filling defect due to gastritis appears to be stiff, then careful repeated observations are needed, correlated with the clinical state and with the gastroscopic appearances; it may still not be due to malignant disease. It is difficult to distinguish some forms of hypertrophic mucosa from multiple polyps. Indeed, hypertrophic gastritis may take that form as described on p. 6, though it rarely does so. In cases which bleed other causes of hæmorrhage, local and constitutional, will need to be considered. Kantor (1936) writes that exploratory operations may be minimized by better acquaintance with the clinical, pathological, and especially the X-ray, manifestations of advanced localized hypertrophic gastritis.

Treatment

The stomach is a long-suffering and adaptable organ, and its local inflammatory diseases respond remarkably to treatment, which has two parts, first, to correct insults and harmful demands; secondly, to apply remedial measures. Relief from swallowed septic material should be obtained and any general cause of ill-health corrected so far as possible. The amount, kind, and frequency of food to be prescribed are individual matters, and especially so with achlorhydria. The patient's experience is in the first instance a valuable guide. In other states with subacidity well seasoned foods may help the appetite, but as a general rule in this form of gastritis, though not always, bland diets suit best, such as the plain mixed diet used after peptic ulceration, with milk and milky foods. If indigestion is obstinate a fluid diet may be taken for a time. Frequent small meals help some patients, but others are better with longer intervals. The tolerance of fat is particularly personal. We give fruit purée and sieved greens to nearly all, and encourage those with adequate teeth to chew the food well themselves. A little good pastry is often not harmful. A few of these patients have rested in bed for a week or two, if overtired, but most are about, taking prescribed walks. If nutrition has suffered the patient rests in the day, before the chief meals, 12 to 1 and 6 to 7 p.m. Alcohol is avoided as a rule. In some, in whom alcohol has played no part as a cause, dilute whisky, $\frac{1}{2}$ to 1 oz. in 7 oz. of water before dinner, may help the appetite, acting as does an alcohol test meal.

After haemorrhage the early stages of gastric ulcer diet with egg and milk or modified milk (Spriggs, 1940) are followed, and vitamins, iron, and building-up measures prescribed.

The most valuable physical measure is to cleanse the stomach by lavage. In former days the direct method with a tube was used. It is nearly 30 years since the first cases in which I saw the gastric juice regain acidity with regular lavage. Occasionally the tube is used still, as it was in Case 64 until the return fluid became clearer. Otherwise, except in cases of obstruction, we use the gastric 'self-lavage'. A pint or thereabouts of warm water containing a small teaspoonful of bicarbonate of soda is drunk at the beginning of the rest-hour, an hour before a meal. The patient lies for 20 to 30 minutes on the left side and then for the same time on the right side. Sometimes rather less bicarbonate is used. One or two patients, for example Case 50, with a sensitive stomach, have been better suited with normal saline. If septic material is swallowed or there is much mucus or epithelial debris, weak peroxide of hydrogen 1 dr. (10 vols.) to the pint, increased gradually to 4 dr., may be used. When the patient returns home gastric 'self-lavage' is easily continued, usually in the evening only. An additional advantage in the home is that the procedure calls for a regular rest hour.

In patients with stomachs the glands of which have undergone the degeneration described above, with formation of abundant goblet cells and

much white mucus, lavage is especially valuable, and may be the chief means of keeping them in a degree of health and comfort. That was so in some of our cases, the patient returning to the treatment or using it more often if discomfort recurred. A striking example in the literature is that of Myer's (1913) patient, the subject of polyadenoma, with a mass in the stomach like a bunch of grapes, who for years washed out 'amazing amounts of egg-white mucus', with great relief.

Of medicines a mild antiseptic is of value, and especially sulphocarbolate of soda, 15 to 20 gr. in plain water on an empty stomach. This is given for two or three weeks and then omitted for a time. Dilute hydrochloric acid is tried cautiously and if well tolerated, as it was in some of the patients, continued indefinitely. The usual digestive powders, including alkaline ones, may give relief to some, even when gastric acidity is absent, but they were not so helpful in most of this group as mild carminatives. Iron, cod-liver oil, strychnine, and barbitone were also used as needed.

Surgery. The stomach has been excised for severe hypertrophic gastritis either because of progressive clinical symptoms or because malignancy was suspected. Hurst and Stokes (1926) reported and illustrated a case of hyperplastic polyposis, or gastritis polyposa, similar in some respects to Case 35; Berg (1930), Kantor (1936), and Buckstein (1940) also reported cases like those here described. All were young people, 29 to 36 years; one had wasted and another had bled from the stomach. The operation was justifiable with such extensive disease as is shown by the specimens. The patient of Davis (1940), aged 47 years, in whom a gastro-enterostomy was done, may have been a case of the same nature. Hurst and Stokes's (1926) patient lived for several years and died of a different complaint. The after-histories of the other patients are not given.

Results of medical treatment. These gross swellings can disappear. It may be suggested that the condition progresses spontaneously to atrophy with regression of symptoms. Our patients, however, had been getting worse before treatment was begun, and their symptoms and swellings diminished with treatment and were apt to return or increase if the régime advised was forsaken. These observations justify the conclusion, with which we are satisfied, that the treatment was directly helpful.

The following is an example of progress with treatment, which was followed intermittently at first.

Case 54. Gross hypertrophic gastritis, which seven years later was absent. November 1930. A woman of 37 years (5817), a cook, had complained for over 11 years of epigastric pain and distension, which had no clear relation to food; also eructation, vomiting, and headaches. Symptoms had been allayed by milk diet and bismuth medicine. Examination—fair condition; abdomen tender. Test meal—no free hydrochloric acid (with histamine); much mucus and pus. X-ray—large irregular nodular inroads on the barium shadow about the greater curvature (Plate 6, Fig. 43); this part appears rigid; no niche of a peptic ulcer was found on repeated examinations, then or later. Advised rest, diet, and medication. Soon after suffered a gross

haemorrhage and was four months in general hospital. On re-examination, May, July, and Nov. 1931, much improved, still retching at times, probably not always careful about diet. Achylia, as before, with muco-pus in fluid withdrawn. With X-ray less swelling, though the induration appeared to be spreading up the greater curve. Treatment with dilute hydrochloric acid and pepsin then begun, alkali taken before breakfast only, benefit followed. Six years later, Feb. 1937, still some epigastric pains. Achlorhydria, mucus, no pus. A little blood with the chemical test in gastric content, none in faeces. Haemoglobin 53 per cent., red cells 4,000,000 per c.mm., white cells 9,100 per c.mm. With X-ray, coarse striae (Plate 6, Fig. 44). Diagnosis—atrophy gastritis; hyperchromic anaemia. The former extensive hyperplasia had subsided. The patient was then admitted to the clinic, Nov. 1937, seven years after the first examination, for nearly two months, during which 2 st. 3 lb. was gained. Symptoms were milder. With treatment, the blood recovered to haemoglobin 80 per cent., and red cells 5,000,000 per c.mm. Was discharged well, with instructions for diet, iron pills, and gastric self-lavage.

In the group with ulcer or gastro-enterostomy or both it is remarkable that in Case 50 considering the prolific sub-inflammatory tissue found *post mortem*, with a simple diet, gastric self-lavage twice a day, rest and gentle exercise, complete gastric comfort was obtained within two months. In milder cases in this group complete recovery can occur as in the following patient.

Case 49. A woman of 36 years (7920) gave a nine years' history of discomfort. Two years before admission gastro-enterostomy had been done for duodenal ulcer. Present complaints—gastric discomfort, cruetation, vomiting, weakness with faint turns, and wasting. Examination—septic teeth, no anaemia. Free hydrochloric acid, 30. X-ray—large indurated folds on greater and lesser curves and about the pylorus. Diagnosis—hypertrophic gastritis with gastro-enterostomy. The septic teeth were removed and treatment given for the stomach as described above. Improved slowly at first, then steadily, fainting turns ceased and digestion relieved; was seven weeks in clinic. Régime drawn up to be followed. Six years later is well and eats anything. Takes milk at bedtime, 'otherwise would lose weight'. Instead of two maids and a governess has a daily help. Two children at home. Works from morning till night.

In the non-ulcer group the association of shrinkage of large folds with deterioration in the gastric acidity in three patients has been noted. Clinical recovery was seen also in patients who were achlorhydric throughout, such as Case 54. Plate 1, Fig. 45 is from Case 62, also achlorhydric. A former exuberant mucous membrane was seen with X-ray to have subsided after three years and gastroscopy showed a dense flat mucous surface. There was a luetic history, but the Wassermann test was negative on admission and had been so for years before.

Sixteen of the 19 were treated as in-patients; in all clinical improvement occurred, and in 12 apparent recovery. In seven the improvement was confirmed by re-examination with X-rays or gastroscope, or both.

The progress of 17 of the patients was followed for from 4 to 14 years, one for three years and one for one year. The recent condition of all is known.

Four of the 19 patients have died, Case 47 after gastric operations, Case 50 after a cerebral thrombosis, Case 56 with encephalitis, and Case 55 of a growth of the colon. Fifteen patients are alive and 14 are known recently to have been well and active. One, a psychasthenic with a luetic history, is complaining, but not of the stomach. All need reasonable care in mode of life and diet.

Prognosis

In earlier patients the future of these large polypoid masses was regarded with apprehension, but the event, in this small series at least, has not justified those fears. I remember well my surprise at finding, with the treatment outlined above, gradual diminution of the masses with repeated observations over 15 months. In our experience relief can nearly always be expected and in most clinical recovery; and if the mode of life can be controlled, the outlook is likely to be satisfactory. Neither adenoma nor carcinoma, such as is ascribed to other forms of chronic inflammation of the stomach, has developed in the group, nor have I found it reported in discussions of this type of gastritis.

Summary

The clinical features of polyps of the stomach and polypoid gastritis are discussed, and the radiology, gastroscopic appearances, pathology, and histology of both are illustrated by radiographs, drawings, and photographs. The clinical and pathological material observed is tabulated in Appendixes.

I. A polyp of the stomach is usually either a papilloma or adenoma, or a leiomyoma. Ten cases were diagnosed radiologically in the course of the X-ray examination of 4,424 consecutive patients, and an eleventh case, of a polyp in the duodenum, was revealed at operation. In the same period there were 104 cases of malignant growth of the stomach and 570 of peptic ulceration.

Thirty-five other cases of gastric polyps with a clinical history are described which have been communicated by colleagues. The clinical details are compared with those of 54 patients mentioned in the literature in which authors described their own cases. This allows of a review of the symptoms and signs of 100 cases. Twenty-four specimens without a history, from pathological museums, are also tabulated.

The term polyadenoma or the general term polyposis is used when there are many, that is, not easily counted, adenomata or polyps. Two varieties of polyposis are described, and an account is given of the symptoms in 19 such cases. In a case of polyadenoma successfully treated by surgery, the X-ray, excised specimen, and histology are shown.

Small tumours away from the pylorus may cause no symptoms. If there are many the condition may be symptomless, but usually is not. In other cases the symptoms are of dyspepsia, especially if there is prolapse into the pylorus, or of gross haemorrhage or silent bleeding, with anaemia, if the

tumour becomes necrotic or ulcerated; or both dyspepsia and haemorrhage. A variable dyspepsia was present in half the cases and bleeding in a third.

Polyps are prone to malignancy. Such a change was reported in between 1 in 5 and 1 in 6 of the series.

The diagnosis of a polyp or polyps is made by radiology and in suitable cases by the gastroscope. There is little or no change in the peristalsis, motility, or contraction of the stomach, unless the pylorus is obstructed.

Similar symptoms occur from polyps of varying pathological nature. The possibility of such a diagnosis should be considered in cases of unexplained anaemia. Gross haemorrhage is suggestive of either leiomyoma or polyposis.

When there is haemorrhage or persistent dyspepsia, or the polyp is large, a wide excision of the tumour and a large area of its base, that is, usually a partial or subtotal gastrectomy, is desirable, provided the condition of the patient allows. Suitable pre-operative treatment, including transfusion, may be needed.

Polyps causing no symptoms, or symptoms which have yielded to medical treatment, or occurring in persons unfit for operation, have in six cases been under observation for years without mishap. Most patients with polyps do not die of them.

II. Polypoid hyperplastic swellings of the gastric mucous membrane were observed in 19 cases, in seven of which there was gastro-enterostomy or past or present peptic ulceration. In three of the remaining 12 cases there was evidence of excess of alcohol. Swallowed septic material was an obvious cause in one and a probable cause in two others. During the same period a diagnosis of gastritis was made in 470 cases.

All the 19 patients complained of dyspepsia, with an inconstant food relation.

In those with peptic ulceration, free hydrochloric acid was usually present in the gastric juice. The histology of the gastric epithelium differed in a superacid from that of a low or non-acid case, the latter showing much degenerative change. In nearly all cases without ulceration free hydrochloric acid was absent or low. In three patients progress towards achlorhydria was noted over two to five years, and was compatible with clinical improvement.

With correction of the mode of life and with the treatment described the swellings and the symptoms subsided in most cases. The patients were all observed or reported upon at intervals for several years.

We record our thanks to many kind colleagues. The writer has been fortunate in the interest of Prof. M. J. Stewart who read the paper, made valued suggestions, and gave help with the histology; also of Prof. T. B. Davie who, in addition to supplying material, supervised in his laboratory Mr. Kidd's skilful drawings of the microscope sections. Numerous others, as acknowledged in the text and in the Appendixes, have reported cases, sent material, and replied to inquiries. Mr. H. W. Rodgers supplied the gastro-

scopic Figs. 3 and 16 and Mr. Howell Hughes Fig. 4. Dr. Picton Davies made the gastroscopic examinations of our own cases. Dr. S. W. Patterson has given help in various ways.

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APPENDIXES

The pathological descriptions of the nature of tumours, size, and other details are quoted as given by the pathologists who kindly sent information or as in the Museum catalogues. When a case in an appendix has been described in the text reference is made to the page concerned in order to avoid the repetition of detail.

PART I

A. EPITHELIAL TUMOURS, SINGLE OR A FEW—WITH HISTORY

Age	Sex	Specimen	History	Treatment	Result	Source	Reference
2	F.	Two papillomata, pyloric antrum and duodenum, malignant change. Transmucosal spread between the two growths. Plate 6, Fig. 21	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Edinburgh: Prof. Learmonth	1222/42
3	M.	Three adenomata, one greater curve and one lesser curve (malignant)	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	G. G.	312/1927
4	F.	Two stalked adenomata on posterior wall; covering mucosa pitted, not ulcerated	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Liverpool: Mr. C. Wells	257/1931
5	M.	Two polypoid cancers, anterior and posterior walls near greater curve. Adenoma on posterior wall	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	London Hosp.: Dr. D. Hunter	330/2
6	M.	Large polypoid ulcerated tumour, on greater curve invading wall, and a few small polyps	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Newcastle: Prof. Shaw	674
7	M.	Six polyps in stomach. Sparsely looks healthy white polyps showing colon pseudomelanotic colon	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Guy's Hosp.: Mr. Davies-Colley	677
8	F.	Greater curve and anterior wall. Mucosa and a few soft shaggy masses on greater curve and anterior wall. Pseudomelanotic colon	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Guy's Hosp.: Mr. Davies-Colley	678
9	M.	Caustic growth, 1½" x 1", 4" above pylorus	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Guy's Hosp.: Mr. Davies-Colley	K. 41
0	M.	Rounded elongated adenoma—near pylorus	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Middlesex Hosp.: Dr. Searff	—
1	F.	Sessile lobulated dark polyp, near pylorus	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	St. George's Hosp.: Dr. J. F. Taylor	H-xiv. 29
2	M.	Polyp, pyloric antrum. Innocent, but was not lymph-gland	See p. 22. Loss of weight. Achlorhydria, occult blood. X-ray—filling defect in pyloric antrum and duodenum. Had lost weight, and after food. Achlorhydria. X-ray—filling defect in first part duodenum and one lesser curve (malignant)	Resection	Recovery. m. later	Sheffield: Dr. Harding	—

M. 50	Two papillomata posterior wall, stalked. Looked innocent, but were not. One duck egg, other bean	Pain lower abdomen. Aortic incompetence, moderate myocardial failure. Secondary anaemia. Hb. 60%. Occult blood. No HCl with histamine. X-ray showed tumour and stalk from posterior wall near greater curve	Transgastric resection	Died	Sheffield: Dr. Harding	H-xiv. 30
F. 60	Benign polyp. Suspicious hyperplasia in one gland	Billous attacks with headaches and vomiting, 18 y. Pain under right shoulder blade. Flatulence. Diagnosis of cholecystitis. Hb. 62%. Achlorhydria. X-ray, no evidence of gall-stones. Clear round filling defect 1" from pylorus. Occult blood then found	Tumour excised. Gall-bladder removed—contained many stones	Recovery. No symptoms	Sheffield: Dr. Harding	F. H.
M. 53	Adeno-papilloma 6 x 2 cm., projecting from anterior wall. Impacted through pyloric ring, invaginating wall of stomach. Two other polyps	Died of mitral stenosis. No history of gastric symptoms	—	—	Manchester: Prof. Baker	III. 155
M. 5	<i>Carcinoid tumour:</i> Mushroom-shaped tumour on broad pedicle. Microscopy—carcinoid, with typical cellular morphology	Shown with gastroscope. Plate I, Fig. 16	Excision (Sir Girling Ball)	Recovery	St. Bartholomew's Hosp.: Mr. H. W. Rodgers	—

B. EPITHELIAL TUMOURS, SINGLE OR A FEW—PATHOLOGICAL SPECIMENS WITH NO HISTORY

F. 54	Two papillomata on posterior wall of fundus, one lesser curve, and one posterior wall by pylorus	—	—	—	Cardiff: Prof. Duguid	3 F. 841
M. 47	Labulated adenoma, 1" from pylorus. Thick pedicle	—	—	—	Mr. Wentworth Charing Cross Hosp.:	—
	Sessile hazel-nut tumour, appearance of papilloma	—	—	—	Dr. Vines Dundee:	—
	Walnut-sized cauliflower tumour, appearance of papilloma	—	—	—	Prof. Cappell Dundee:	—
	Stalked adenoma, 1½" long, smooth surface, on greater curve	—	—	—	Prof. Cappell London Hosp.:	580/1926
F. 54	Polyp, ½" diameter with ¼" stalk, on lesser curve	Run over. Fractured base of skull and jaw. Died shortly after admission	—	—	Dr. D. Hunter London Hosp.:	380/1927
M. 47	Adenoma, fundus	—	—	—	Dr. D. Hunter Manchester:	III. 153
	Stalked adenoma, 2-4 x 1 cm.	—	—	—	Prof. Baker Manchester:	III. 154
M. 60	Stalked adenoma—ulcerated, septic. Middle of lesser curve. A cancerous ulcer near pylorus	Died, acute suppurative meningitis	—	—	Prof. Baker Newcastle:	333/3
F. 60	Stalked adenoma, ½ x ¼", in fundus. Purple—? torsion	Died, cirrhosis of liver. Similar tumour in rectum	—	—	Prof. Shaw Mr. Alderwood	34. 751 A
M. 61	Pigmented papilloma, flattened, stalked, 1" x ½" x ¼", in fundus	Cancer of oesophagus. Secondaries in liver	—	—	Dr. J. F. Taylor St. George's Hosp.:	34. 752 A
			—	—	Dr. J. F. Taylor	

Sex	Age	Specimen	History	Treatment	Result	Source	Reference
M.	70	Two tumours, large and small walnut, flattened. One has a stalk, hypertrophied mucous membrane	Admitted comatose. Died next day from cerebral haemorrhage, atheroma	—	—	Guy's Hosp.: Mr. Davies-Colley	670
F.	63	Pyloric part rugous, several small warty dark papillomata growing on folds	—	—	—	Guy's Hosp.: Mr. Davies-Colley	670 ¹
C. POLYPOSIS WITH HISTORY.							
			6 m. nausea and vomiting. Jaundice.	—	—	Glasgow: Sir R. Muir	6579 Mus. IV. 61 a
			Alcoholic history	—	—	Liverpool: Prof. Davio	M. 4562
M.	62	Size up to a cherry; some stalked. Minute elevations near lesser curvo in row, corresponding to rugae. Cancer in body, with middle. Cancer in liver secondaries in liver	10 y. vague dyspepsia. Appetite good. High gastroctomy. Also several polyps ligated and removed (Mr. Kirk Wilson)	Recovery. 3 y. later, macrocytic anaemia, resistant to liver. Ventriculin effect	—	London Hosp.: Dr. D. Hunter	187/1034
F.	53	See p. 16. Papillomata, size large pea, general except pylorus and cardia	4 y. after examination, suprapubic prostatectomy	—	—	—	—
M.	57	Many stalked adenomata, middle of stomach, mainly greater curvo. Surfaces of some thick and indurated, no ulceration	8 y. before, intermittent strangulation. Pancreatic cyst drained. 6 y. vomiting and epigastric pain. 4 y. before, stomach and achlorhydria. Found full of fluid, and achlorhydria. X-ray—filling defects greater curve—cancer suspected. P.M., carcinoma prostate and endocarditis	Transfusions. Partial gastroctomy (Mr. Ewart)	Good recovery	St. George's Hosp.: Dr. J. F. Taylor	34. 751 B
M.	57	Mostly prepyloric, largest dumb-bell, sessile, lobulated, 2½" x 1½". Many smaller, on area 2" diameter, proximal to large tumour. Adenomata	Regurgitation for years, lassitudo 13 m. Hb. 37%. Occult blood	Recovery. Wollity. later	—	St. Mary's Hosp.: Prof. Newcomb	34. 752 ²
M.	0	Many freely movable adenomata. Largest attached to fold on greater curvo, could be brought into pyloric opening	2 y. vomiting after food, and acute pain. Palpable lump below and left of navel. X-ray—filling defect, all pyloric region	Partial gastrectomy up to Recovery	—	Guy's Hosp.: Mr. Davies-Colley	675
F.	63	Three lobulated small walnut-sized polyps, 12 smaller. Some blood-stained	No family history of polyposis. Never indigestion. Neither smokes nor drinks. Hb. 50%. Achlorhydria, much mucus. W.R. and Kahn negative. X-ray—filling defects. Gastro-scope—polyposis	Transfusion Hb. 80%. Gastroctomy	—	—	—
M.	62	Many slight mamillations	Cramps, pains, right abdomen, tenesmus. Operation for ovarian cystoma. Died 14 days later	—	—	Belfast: Prof. Young	A. 899
F.	38	Small pedunculated adenomata, also smaller sessile ones. Cancerous ulcer, fundus. Cystoma probably undergoing malignant change	* Case 31 was reported by Gago (1937)	—	—	—	—

F. 39	Pathological report: 'Chronic gastric catarrh, with multiple polypi. Microscopically the polypi show chronic inflammatory hyperplasia of the mucosa, with abundant infiltration of polymorphs, lymphocytes, and plasma cells. The hyperplasia appears to be superimposed upon an adenomatous element.'	History of extraction of teeth for pyorrhoea. Poor appetite and loss of weight. Achlorhydria, blood, also occult blood. X-ray—polyposis. Hb. 66 %	Partial gastrectomy (Mr. John Anderson)	Good recovery	Dundee: Prof. Cappell	20124
F. 63	Sec p. 16. General polyposis, hyperplastic	5 y. wasting, anaemia. Tumour. X-ray 1939, polyposis, ? malignant. With treatment, vomiting ceased, pain at times. 1942, gross haematemesis. Hb. 30 %. X-ray—polyps no longer seen. Gastro-scope: congested atrophic membrane	Transfusion. Iron	Improving	Oxford: Dr. Hobson	Mrs. C.
D. POLYPOSIS WITH NO CLINICAL HISTORY						
	Numerous polypoid adenomata, projecting, chiefly about greater curve	—	—	—	Cardiff: Prof. Duguid Mr. J. E. Wentworth	34. 841
	Most of stomach covered with smooth polyps, stalked and sessile, 1" or 2" free near cardia and pylorus	—	—	—	Dundee: Prof. Cappell	—
F. 63	Polyps mostly about body. One finger-like process on broad base. Also large folds near pylorus. Mucous membrane between looks normal	Died of pneumonia	—	—	Edinburgh: Prof. Drennan	—
F. 80	Stalked and sessile adenomata about greater curve	Died of chronic nephritis and broncho-pneumonia	—	—	St. Mary's Hosp.: Prof. Newcomb	34. 7521
	Multiple benign polyps accidentally found at autopsy	—	—	—	Sheffield: Dr. Harding	H-xiii. 2
	Multiple polyps, no history. Sections throw doubt on innocence	—	—	—	Sheffield: Dr. Harding	H-xiii. 2
M. 62	Numerous apparently innocent polyps, and large polypoid carcinoma. Metastases in liver and glands	Died of gangrene of lung	—	—	Sheffield: Dr. Harding	H-xiv. 27
	Polyposis—from a lunatic	—	—	—	University College Hosp.: Dr. L. E. Glynn	—
	About a dozen small smooth polyps within 2" of pylorus. Three or four stalked, others sessile	—	—	—	Dundee: Prof. Cappell	—
M. 63	Sessile leiomyoma	Thrombosis aorta and left brachial. Arm swollen, cold and pulseless. Died next day. Nausea 2 w., and severe vomiting a few days. T=100° F. P=132	—	—	Cardiff: Prof. Duguid Mr. J. E. Wentworth	34. 831
		E. MYOMATA				

No	Sex	Age	Specimen	History	Treatment	Result	Source	Reference
7	F.	37	Growth outside stomach; removed, leiomyoma. Recurrences inside stomach—two growths	See p. 27. Pain after food, relieved by vomiting. No haemorrhage. Gall-stone colic was suspected	Excision	Recovery. Recurrence 4 y. later. Excised. Died 2 y. later, with functional changes in liver	Liverpool: Sir R. Kelly	Mus. Ao. 37
8	F.	42	Size of golf-ball. A little lobulated, stalked. Mucous membrane near rugous and injected	Severe irregular dyspepsia, several years. Watery. Gastric juice subacid; mucus, blood. X-ray—large filling defect of body	Excised with good margin of mucous membrane	—	Guy's Hosp.: Mr. Davies-Colley	673
9	F.	25	Myoma, $2\frac{1}{2} \times 1\frac{1}{2}$ ", some haemorrhage in it. Body of stomach	Sudden haematemesis, after which vague epigastric discomfort, relieved by food. While under treatment in hospital as gastriculcer, second larger haematemesis. X-ray—filling defect mid-stomach	Excision	Recovery. High normal gastric acidity	Guy's Hosp.: Mr. Davies-Colley	670
10	M.	67	Tumour $1\frac{1}{2}$ " diameter. Projects under mucous surface. Lesion at summit	7 w. epigastric pain. Repeated vomiting black fluid. Frequent stools. Movable tumour felt under left rectus	Excision with fringing of mucous membrane (Mr. Rowlands)	Recovery	Guy's Hosp.: Mr. Davies-Colley	681
11	M.	47	Myoma, projecting from both serous and mucous surfaces, near cardia. Longitudinal chronic ulcer on gastric pathway, and two more on end of tumour	20 y. indigestion. 9 m. ago, severe epigastric pain, then well for 3 or 4 m. Previous 6 m., loss of appetite, weight, and strength, and shortness of breath. Some epigastric pain. No dysphagia. X-ray—smooth lobulated tumour encroaching on air-bubble—confirmed by Ba meal. Extended as filling defect in gullet $1\frac{1}{2}$ " above diaphragm	Resection through gullet and stomach. Stomach joined to gullet in chest (Mr. Brock)	Good recovery 9.2.42	Guy's Hosp.: Mr. Davies-Colley Mr. Brock	42, 21
12*	M.	37	Fibromyoma, posterior wall $4\frac{1}{2}$ " above pylorus. Size golf-ball, pale, three purple-black depressions. Capsule, pedicle. Peritoneum dark, as if haemorrhagic there. Microscopy, probably low malignancy	After a fall, indefinite pain and indigestion for 3 m. No wasting. 17 days before, severe pain, back and abdomen, dizzy. 14 days before, melæna and later haematemesis and collapse. Delirious and unconscious on admission. Hb. 25%. Died fourth day	—	Died	Westminster Hosp.: Dr. Haines	P. 16
13*	F.	50	Golf-ball size leiomyoma, anterior wall $2\frac{1}{2}$ " from pylorus	Well till 11 days before. Haematemesis, melæna, collapse. Admitted as gastric ulcer, died in 3 days	—	Died	Westminster Hosp.: Dr. Haines	P. 17
14	F.	67	$2\frac{1}{2}$ " diameter. Capsule, surface ulcerated, piece of wall around. Microscopy, whorled fibrous tissue and muscle	1936, haematemesis. Chronic gastric ulcer diagnosed. Treated and discharged. 1937, melæna. X-ray—filling defect of fundus. Confirmed with gastroscopy	Sleeve resection	Stormy convalescence. Recovery	Middlesex Hosp.: Dr. Scarff	V. 13
15	F.	59	$4 \times 1\frac{1}{2}$ ", sausage shape, in fundus. Normal mucous covering with ulcer at dip on summit. Lay between mucous membrane and muscularis mucosae. Soft fibroma	3 m. epigastric pain. Vomited large quantities after food. No blood. On admission vomiting constant. Contained no free HCl. Lactic acid, fungi present. Left epigastrium tender. Movable tumour about the navel	Removed	Died	Westminster Hosp.: Dr. Haines	P. 15
16	F.	61	Submucous intramural myoma, with adjacent, though distinct and separate, spherooidal-celled carcinomatous ulcer	Temporary indigestion 1 y. before. 5 m. ago epigastric pain 1 hr. after food, relieved by food, for 3 w., culminating in perforation through an indurated patch on anterior surface. Operation, recovery.	Subtotal gastrectomy	Recovered and gained weight. Later extension to colon and died in 6 m.	Edinburgh: Prof. Learmonth Prof. Dreumun	J. L.

Three X-ray examinations at intervals, at the last of which suspicion of carcinoma, and opinion given that a benign tumour seemed also to be present (Dr. McWhirter). Admitted under Prof. Learmonth and diagnosis confirmed at operation

* Cases 42 and 43 were reported by Gossage and Hicks (1914).

F. LIPOMATA

M.	66	Spherical capsulated tumour on greater curve, nearly 2" diameter. Beneath mucous membrane in line of attachment of greater omentum	Street accident. Died from injuries in 6 w., acute bronchitis	—	Guy's Hosp.: Mr. Davies-Colley	679
		Submucous lipoma, 1" x 1"	—	—	Middlesex Hosp.: Dr. Scarff	K. 40. 4

PART II

G. HYPERTROPHIC AND OEDEMATOUS GASTRIC SWELLINGS

no	Fol.	Year	Sex	Age	Other diseases	Clinical account	Gastric juice HCl (index)	Treatment	Later history
<i>our cases after gastro-enterostomy:</i>									
7	1704	1921-39	M.	43	—	See p. 35. For 35 y. intermittent indigestion with ulcers, operations and perforations. Superaeid throughout Over 10 yr. indigestion, duodenal ulcer, perforated. Hb. normal. W.R. negative. Nausea, poor appetite. Large swellings round stomach, and jejunal ulcer	82, 1921 80, 1937 94, 1939 40	Medical and partial gastrectomy	Died 2 y. later after operation for gastrocolic fistula
8	5713	1930-35	M.	46	Shell shock. Gun-shot wound. Lucas	See p. 44. 9 y. history. Swellings greater and lesser curves, and pylorus	30 Mucus	As on pp. 42 and 43	Improved and returned to work abroad. Has reported since
9	7920	1936	F.	36	Septic teeth. ? Vaso-vagal attacks. Low B.P.	See p. 36. 21 y. history. Very large swellings	6 (before admission) Mucus, trace blood	As on pp. 42 and 43	Recovered. Now well
0	8751	1939	M.	62	Malaria			As on pp. 42 and 43	Symptoms ceased. Died cerebral thrombosis later
<i>our cases after peptic ulcer:</i>									
1	7590	1935	M.	42	Family history, peptic ulcer	22 y. intermittent indigestion, duodenal ulcer. Loss of weight. Hb. 80%, red cells 5,000,000. Gross swellings above pylorus. Duodenum scarred	100 Mucus	Advised	Improved. Wall 6 y. later
2	7722	1935	F.	46	Piles	See p. 35. 2 y. history, indigestion, headache. Hb. 55%, red cells 3,600,000. Nodular polypoid masses near pylorus	70 Mucus, pus	Rest, diet, self lavage, iron	Improved. 2½ y. later obstruction at pylorus. Operation. Growth diagnosed. Gastro-enterostomy. Is well 3½ y. later Improved
3	9501	1941	M.	45	Aortic regurgitation. Pathological gall-bladder	10 y. intermittent pain, gastric ulcer formerly. Now swellings and coarse rugae mid-stomach, confirmed by gastroscop	5 Mucus	Rest, diet, self lavage, atropine, phenobarbitone, hexamine, bile salts	

[illegible]

urec cases after excess of alcohol:

3	8611	1038	M.	62	Appendicectomy 3 y. before. Business strain. Unmarried. Lives in hotel. Depressed. Diverticulosis	Pain about caecum, after food. Tender terminal ileum. Large nodular swellings on greater curve, near cardia	0 Mucus, pus	Reduction, then abstinence, diet, rests, and exercise	Slow continuous improvement with readmission over 2 y. Nodules diminished, still coarse folds. Recovery
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4	8958	1939	M.	44	Gun-shot wound. War (1914-18). Headaches. Neurasthenia	4 y. attacks nausea and vomiting, worse after food. Loss of weight. Large nodular swellings about cardia	25, 1939 85, 1940	As on pp. 42 and 43. Direct lavage with tube at first, then self lavage	Recovered. Some recurrence with alcohol (with Home Guard). Four admissions in 2 y. Swellings less. Condition good
5	8672	1938	M.	57	Bronchitis, pneumonia, diverticulosis. Lives alone	2 y. miserable, gastric pains, poor appetite, constipation. Morning cough. Test meal failed. Whole stomach polypoid mucosa	—	For bronchitis and stomach	Recovered and returned to work

H. TWO PATHOLOGICAL SPECIMENS SHOWING GASTRITIS

no	Sex	Age	Specimen	History	Source	Referenco
3	M.	43	Mucous membrane thick, big folds, mamillated. Tenacious mucous on surface, no ulcers or scars. Magenstrasse fairly clear. Plate 8, Fig. 36	Died after street accident. Alcoholic. Abdominal pain frequent, on account of which had to leave off drink for a day or two. Eructation. Loss of appetite	Guy's Hosp. Mr. Davies-Colloy	621

hypertrophic gastritis after ingestion of septic and irritating substances:

7	M.	50	Rugous and warty elevations all over except cardiac t. No formed polyps. Hypertrophic mucosa and submucosa. Plate 8, Fig. 37	Former phthisis. Swallowed rubbish, occasionally vomited. Scars on penis. Died in asylum	Guy's Hosp. Mr. Davies-Colloy	6681
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DESCRIPTION OF PLATES

PLATE 1 (coloured)

FIG. 1. Gastrosopic drawing to show pyramidal process of mucosa on the anterior surface of the greater curve. Gastritis was seen elsewhere, but not in this region. $\times \frac{4}{5}$.

FIG. 3. Gastrosopic drawing (Mr. H. W. Rodgers) to show sessile polyp in moderately atrophic mucosa. $\times \frac{2}{3}$.

FIG. 4. Gastrosopic drawing (Mr. Howell Hughes) to show a polyp arising from the greater curve. The patient was a diabetic who had vague epigastric pains. On X-ray polyposis was suspected, but gastroscopy showed only one tumour. $\times \frac{4}{5}$.

FIG. 16. Case 26, p. 51. Gastrosopic drawing (Mr. H. W. Rodgers) to show carcinoid tumour of the stomach. $\times \frac{2}{3}$.

FIG. 27. Case 35, p. 16. Gastrosopic drawing to show congested granular mucosa on anterior wall of the pars media. $\times \frac{1}{2}$.

FIG. 39. Case 57, p. 38. Gastrosopic drawing of the anterior wall of the greater curve to show polypoid gastritis. There are large smooth folds, not injected, and paler than normal; the deep valleys between are filled with mucus. $\times \frac{1}{2}$.

FIG. 40. Gastrosopic view of polypoid gastritis near the angulus (*a* indicates the left pillar of the angulus). There are large bulbous stiff swellings, but not much mucus. From a man of 58 years with hypertrophic gastritis of the body of the stomach and proximal part of the antrum; he also had duodenal ulcers. The gastric juice showed normal acidity. The history was long. The patient was a recent admission and is not tabulated in the present series. $\times \frac{1}{2}$.

FIG. 41. Case 60, p. 39. Gastrosopic drawing to show hypertrophic gastritis, which is improving, but is more congested than that in Case 57. There are pronounced folds on the greater curve. The mucosa is injected. The pattern was not obliterated on dilatation. There was no excess of mucus. $\times \frac{1}{2}$.

FIG. 45. Case 62, pp. 44 and 66. Gastrosopic drawing to show atrophic mucous membrane which was formerly hypertrophic. There is a dense, pale, flat, mucous surface, confirming radiological appearance. X-ray three years before had shown multiple polypoid swellings in this area. $\times \frac{4}{5}$.

FIG. 46. Drawing of papillomata growing upon hypertrophic folds, pp. 32 and 52.

FIG. 7. Case 1, p. 15. Drawing of low-power view of a portion of the pedicle of an adenomatous polyp which is becoming carcinomatous. The malignant tissue in the right upper part of the field is characterized by greatly increased basophilic staining owing to the presence of large and numerous nuclei.

FIG. 8. Case 1. Drawing of high-power view ($\times 325$) of malignant portion of the polyp showing a glandular structure in the upper part and a solid spheroidal-celled carcinoma in the lower.

FIG. 13. Case 3, p. 17. Drawing of microscopic section ($\times 325$) of a leiomyoma. The tumour is composed of stout, spindle-shaped, unstriped muscle cells, partly arranged in strands. Two mitotic figures are shown.

FIG. 14. Case 3. Drawing of microscopic section ($\times 250$) of the more cellular and more irregular part of the growth, showing a wide, very thin-walled vessel running through it.

FIG. 15. Case 3. Drawing of microscopic section ($\times 250$) from an adjacent portion, showing areas of intense oedema.

PLATE 2 (coloured)

FIG. 29. Case 47, p. 35. Drawing of low-power view of stomach to show hypertrophic gastritis. The mucosa is thrown into large thick folds; the glands show fairly regular arrangement. There is hypertrophy of the muscular coat.

FIG. 34. Case 50, p. 36 (also Plate 3, Figs. 31 to 33). Drawing of high-power view of the fundal mucosa to show chronic gastritis (fundal type mucosa). The drawing shows

small round-celled infiltration mainly in the surface zone, with loss of surface epithelium and hypertrophy of the more superficial portion of the crypts.

FIG. 35. Case 50. Drawing of low-power view of the gastric mucosa showing a deeply-seated group of simple undifferentiated glands, many of them cystic. The appearances and the relation to the surface mucosa show an acquired heterotopia. The inset shows better the vegetative character of much of the acinar epithelium.

PLATE 3 (coloured)

FIG. 24. Case 28, p. 16. Drawing of high-power view of section of polyposis of the stomach, showing simple glandular hyperplasia with cystic degeneration of some of the acini. The stroma contains numerous small round cells, mainly lymphocytes and plasma cells. The inset shows a polyp ($\times 2$) with its core of pink-stained tissue.

FIG. 31. Case 50, p. 36. Drawing of high-power view of gastric mucosa to show chronic gastritis (pyloric type mucosa). There is diffuse infiltration of the mucous membrane by small round cells; intense capillary engorgement; and partial loss of surface epithelium. The section shows a cleft between two folds partly filled with mucopurulent exudate.

FIG. 32. Case 50. Drawing of low-power view of section of the edge of a chronic ulcer, with overhanging hyperplastic mucosa. The ulcer has completely breached the muscular coat, its floor being densely fibrous with a thin covering of granulation tissue.

FIG. 33. Case 50. Drawing of section of gastric mucosa, to show chronic gastritis. There is intense infiltration of the mucosa by lymphocytes and plasma cells with atrophy of the secretory glands. The high-power inset shows the tip of a mucosal fold with its stroma overrun with plasma cells.

PLATE 4

FIG. 2. Radiograph to show mobility of stomach wall in hypertrophic gastritis. Above, filling stage with polypoid masses. Below, the stomach is filled normally, as it would not be if a malignant growth were present.

FIG. 5. Case 1, p. 15. Radiograph to show a large adenomatous polyp. Filling stage, showing a pear-shaped mass with pedicle arising in the upper part of the stomach. Outlines are traced in the left-hand picture. The adenoma is becoming malignant.

FIG. 9. Case 2, p. 15. Radiograph to show early polyadenoma. There is a scalloped outline of the greater curve in the pyloric region. Peristalsis passed over this, but was arrested at the site of an ulcer on the lesser curve. The excised part of the stomach is shown in Plate 5, Fig. 10.

FIG. 11. Case 3, p. 17. Radiograph to show a large leiomyoma. Above, filling stage. Below, after more opaque material has entered. There is a large spherical filling defect. The excised part of the stomach is shown in Plate 5, Fig. 12, and the histology in Plate 1, Figs. 13 to 15. The leiomyoma is becoming sarcomatous.

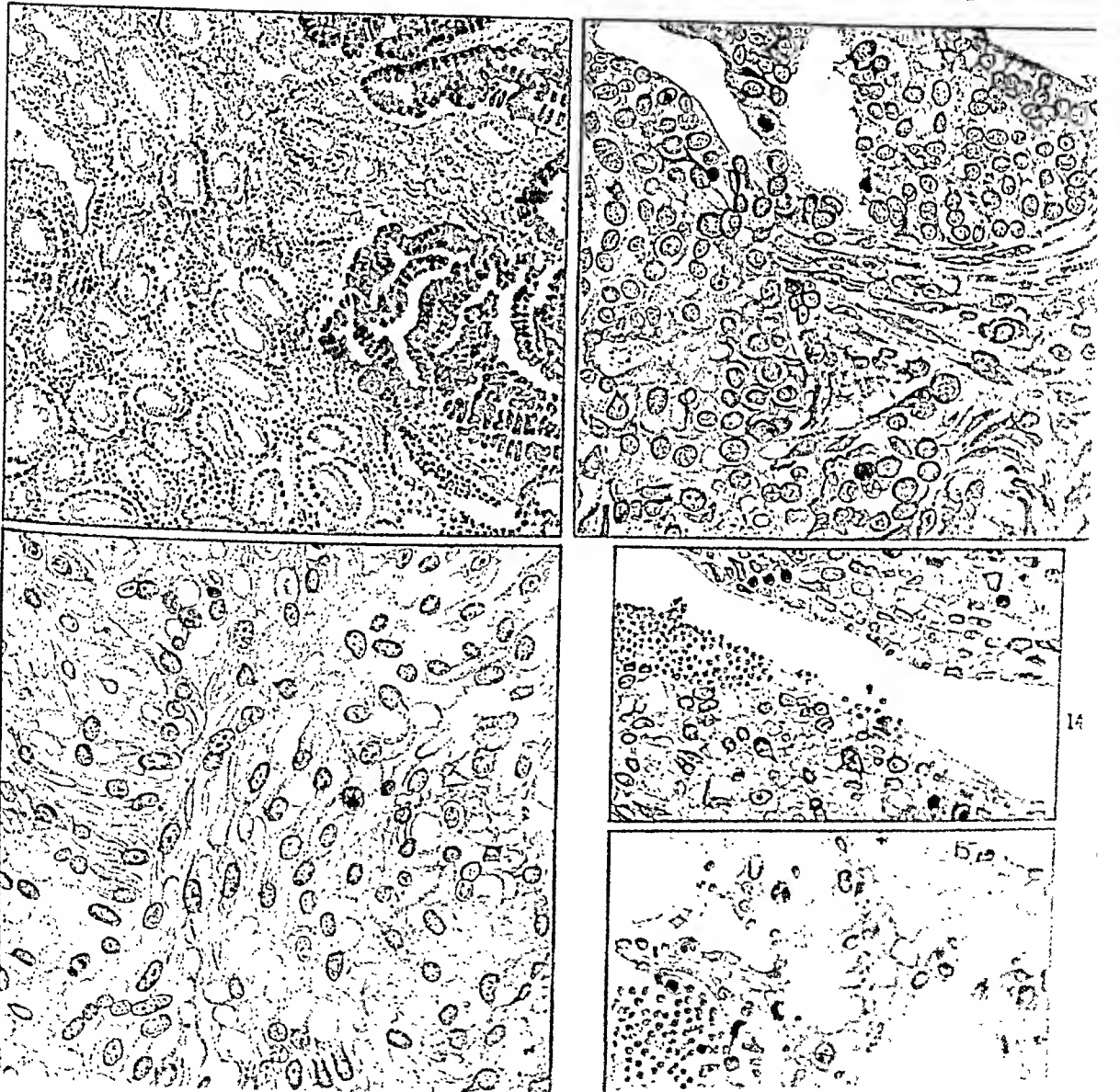
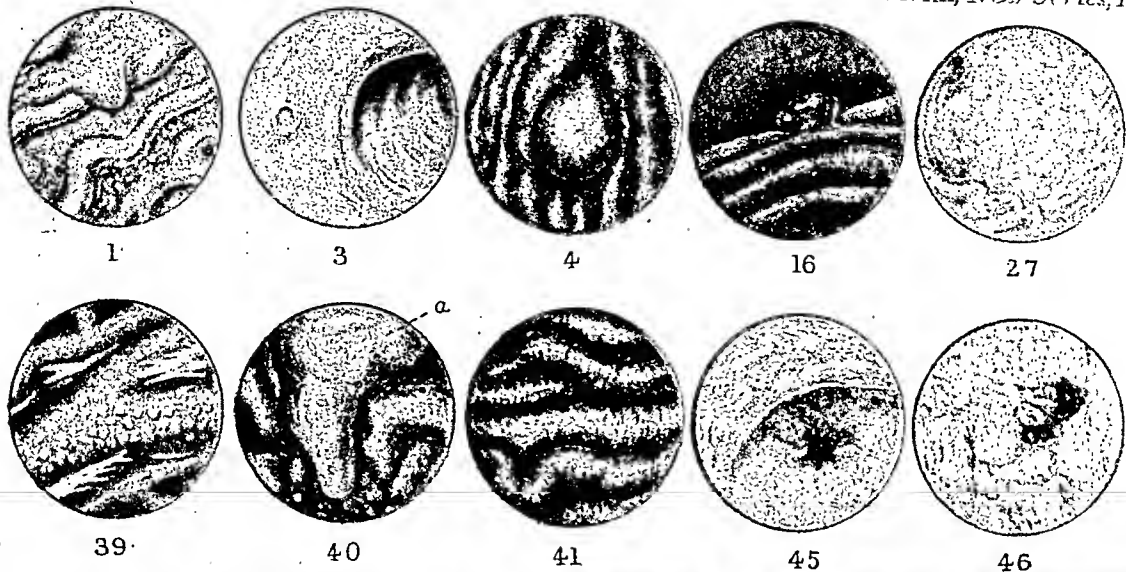
FIG. 18. Case 8, p. 19. Radiograph to show a large pyloric polyp. Left, filling stage, there is a large pear-shaped mass in the pyloric part. Right, immediate prone, showing a normal dilatation at the level of origin.

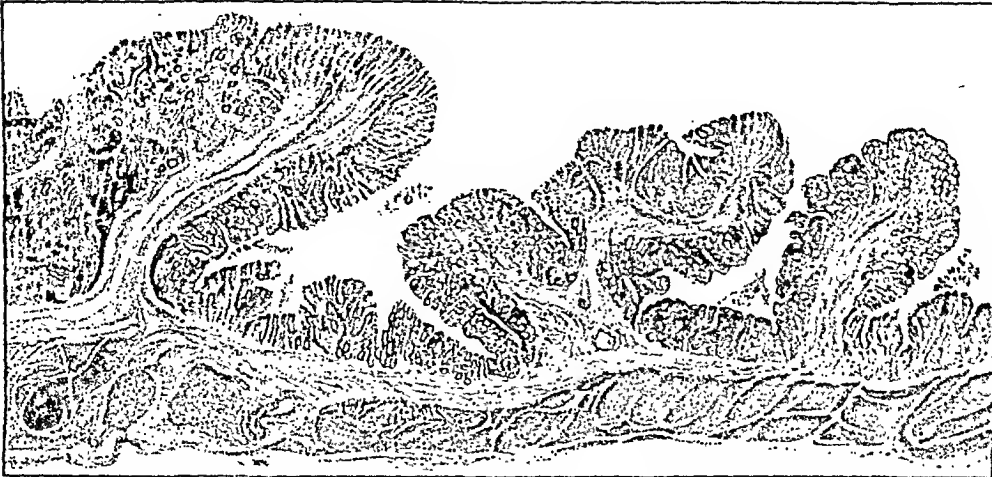
FIG. 19. Case 13, p. 21. Radiograph to show a gastric polyp lying in the duodenum. The filling defect in the duodenum is indicated by the arrows. The adenoma arose in the stomach and had passed through the pylorus.

PLATE 5

FIG. 6. Drawing (by E. M. Wright) of excised part of stomach of Case 1, p. 15. A large pedunculated polyp is seen arising near the cardia. A radiograph is shown in Plate 4, Fig. 5, and the histology in Plate 1, Figs. 7 and 8.

FIG. 10. Drawing (by E. M. Wright) of excised part of stomach of Case 2, p. 15, showing early multiple adenomata, a carcinomatous ulcer on the lesser curve. A radiograph is shown in Plate 4, Fig. 9.

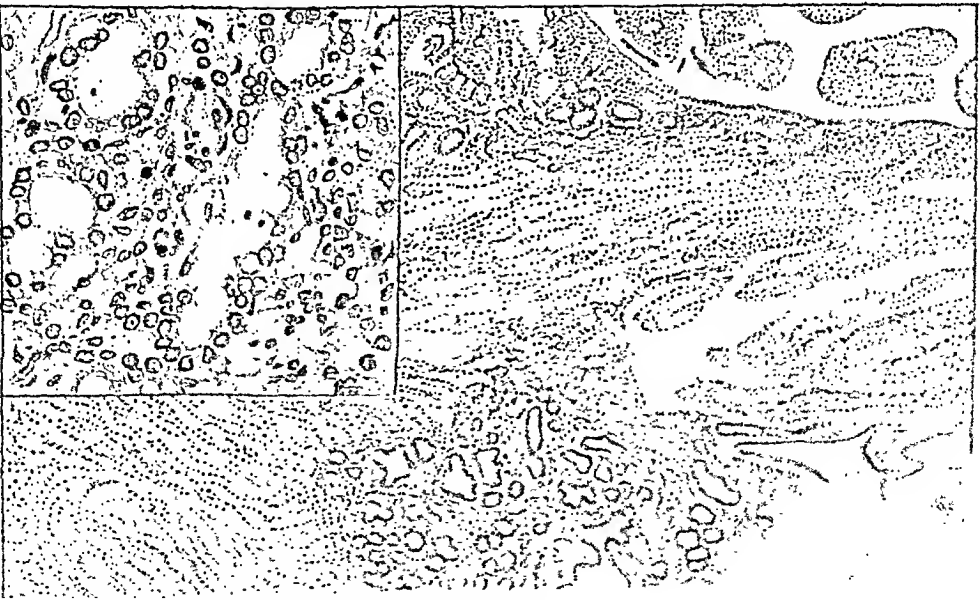




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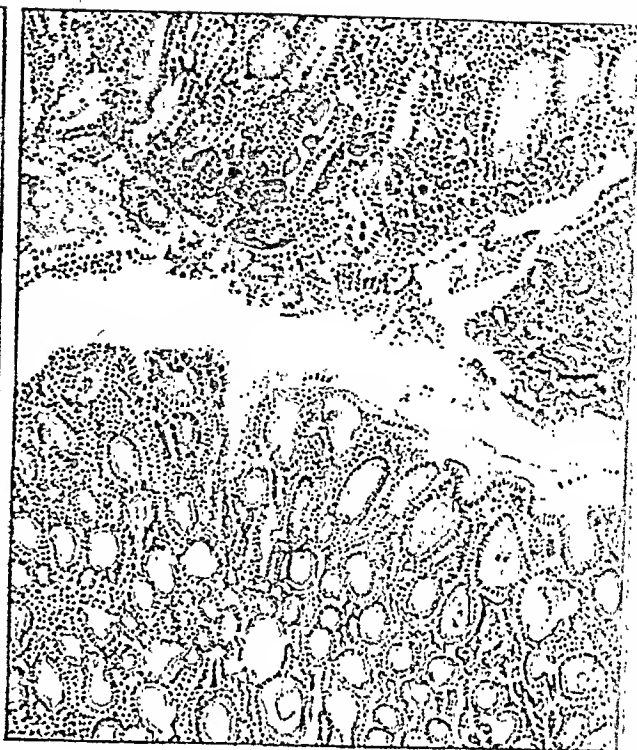


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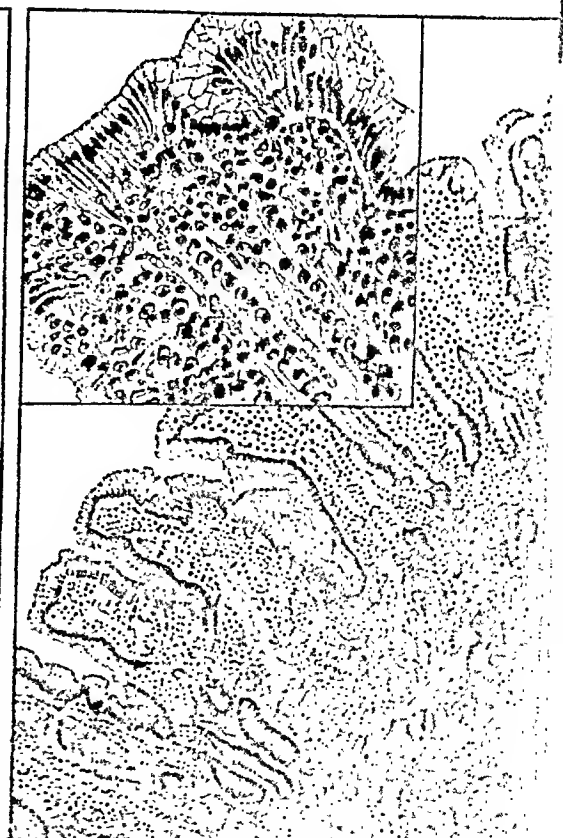


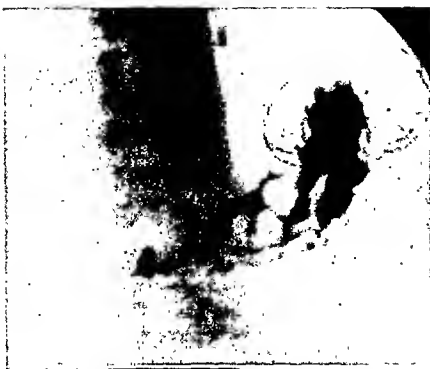


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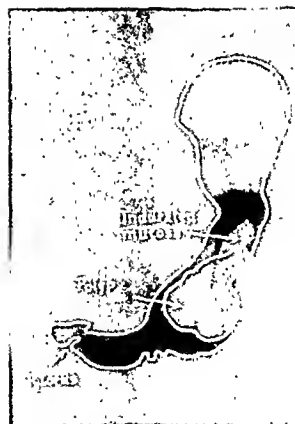
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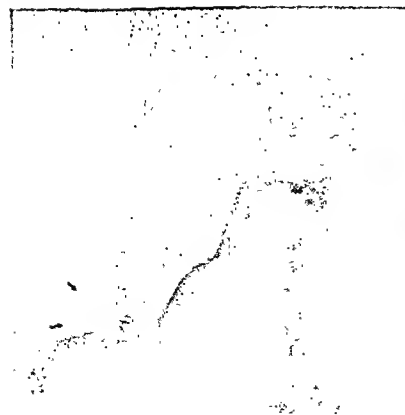
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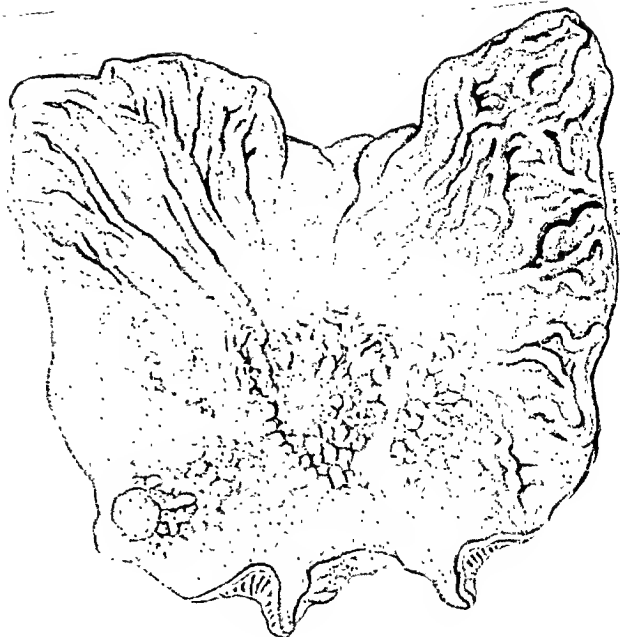


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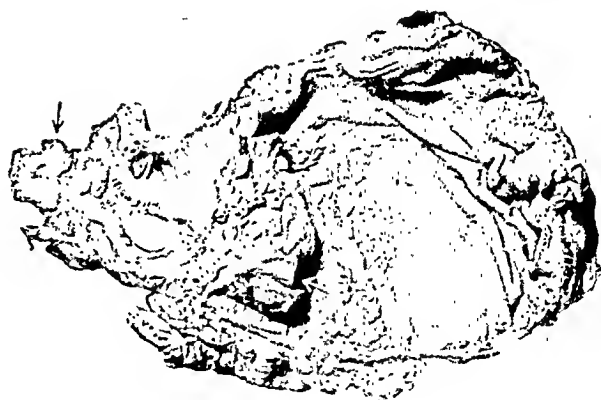
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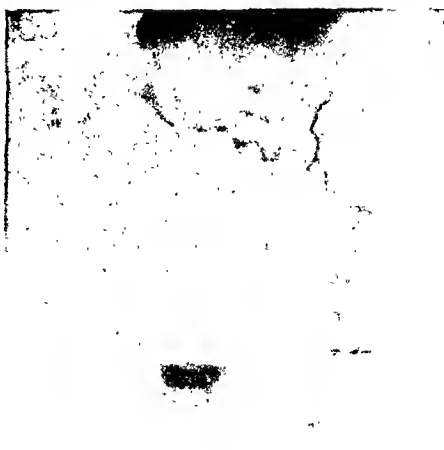
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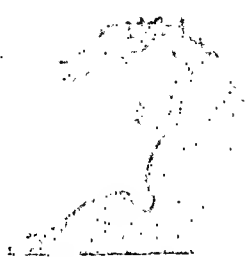


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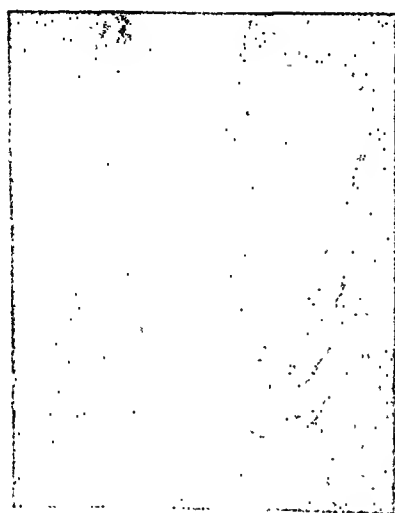
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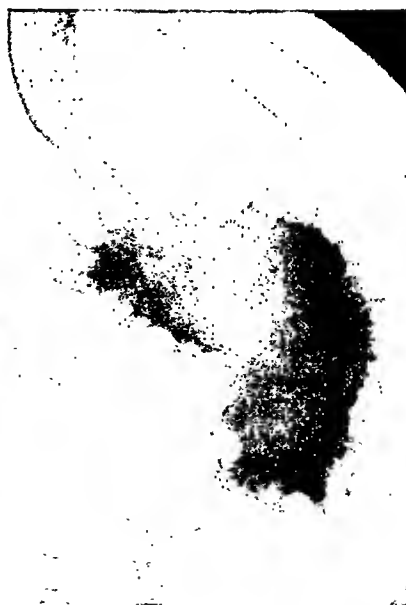
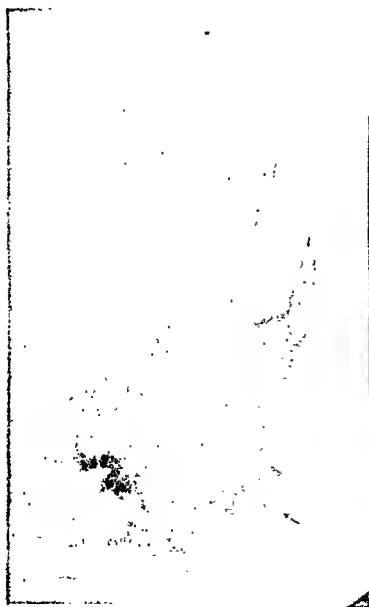
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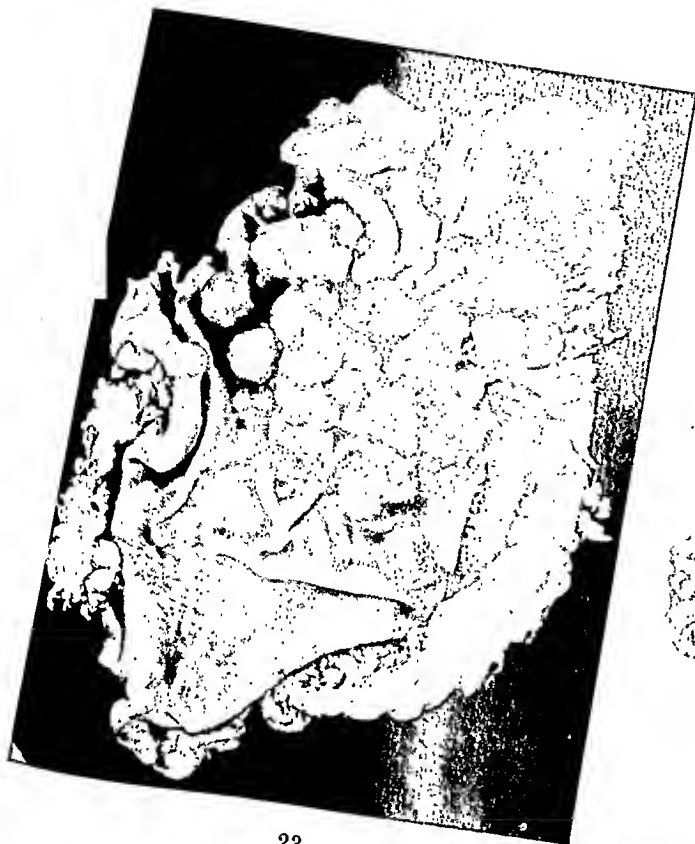
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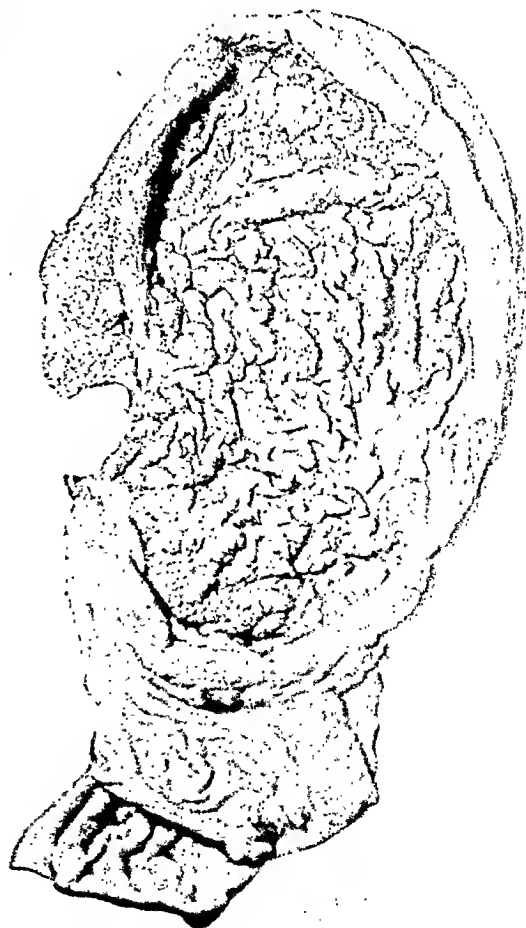
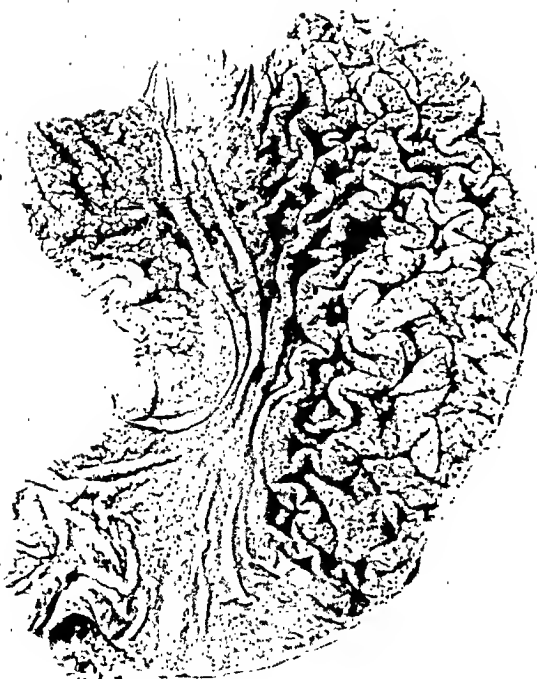
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PNEUMOCOCCAL ENDOCARDITIS¹

BY R. W. LUXTON AND G. STEWART SMITH

(From the Crumpsall Hospital, Manchester)

With Plates 9 and 10

PNEUMOCOCCAL endocarditis, although not often diagnosed during life, is a fairly common condition. The symptoms of acute endocarditis are usually obscured by and attributed to the associated pneumonia. The purpose of the present paper is to clarify the clinical picture, to stress certain features of morbid anatomy, and to indicate the practical points which facilitate diagnosis. Most of the recent literature is American, the last review in this country being by Horder in 1906. Our general conclusions are based on a study of the literature and a review of 20 cases of the disease which have come to autopsy in Crumpsall Hospital, Manchester, during the past six and a half years. In some of the earlier cases, in which the diagnosis was made at autopsy, there are no clinical observations on the size of the spleen and the presence of petechiae; in the later cases the diagnosis was made early, and the clinical course and features of the disease observed with care. A tabular summary of the more important findings is given on page 73. Notes on five cases which illustrate special points are given at the end of the paper.

Aetiology and Morbid Anatomy

Pneumococcal endocarditis is almost always associated with pneumonia, especially lobar pneumonia, but as in Case 20 in this series, the site of the primary pneumococcal infection is not always easy to determine. Thayer (1926) showed that of 96 cases of acute bacterial endocarditis, 13 per cent. were caused by the pneumococcus. Table I (Hadfield and Garrod, 1938) gives an indication of the bacteriological types of this disease. From the somewhat scanty records available it appears that any of the types of

TABLE I
Percentage Incidence of Types of Infective Endocarditis

	Harbitz (1899)	Lenhartz (1901)	Horder (1906)	Clawson (1924)	Thayer (1926)
Streptococcus	53	51	63	74	55
Pneumococcus	15	24	19	11	13
Staphylococcus aureus	25	19	7	15	12
Gonococcus	6	3	3	—	11
H. influenzae (Pfeiffer)	—	—	5	—	4

¹ Received July 22, 1942.

pneumococcus may cause the disease, but Type 1 is the most common. The pneumococcus was typed in 12 of the cases reported here; seven were Type 1, and there was one each of Types 2, 3, 5, 8, and 19.

No valvular lesion has been described as typical of pneumococcal endocarditis. In the standard text-books of pathology the condition is usually described as intermediate between the endocarditis caused by haemolytic streptococci and staphylococci and that produced by the streptococcus viridans, and while there are great differences in the descriptions of the vegetations they are mostly described as massive and destructive, often giving rise to emboli. Most writers agree that the size of the lesion depends almost entirely on the duration of the illness (Hadfield and Garrod, 1938). Preble (1904) after enumerating the many different types of lesion described concluded that none was characteristic; Kerschensteiner (1897), on the other hand, regarded the following features as characteristic:

1. The vegetations are large with a wide base.
2. They are midway between the ulcerative and the verrucose forms.
3. They have a smooth, discoloured surface.
4. There is a tendency towards softening.

In the present series of cases the following features were noted.

1. The size of the vegetations, most of which were large and some massive, was roughly proportional to the length of the illness, which varied from 15 to 71 days.
2. The vegetations (excluding two cases seen early in the series where the descriptions were inadequate) were single, polypoid, and yellowish-green in colour, with a characteristic smooth surface and little evidence of surface ulceration or loose tags. They were larger than the vegetations caused by the streptococcus viridans and less ragged than those due to staphylococci and haemolytic streptococci.
3. Destruction of the valve when it occurred was at the base of the vegetation which often concealed it. In two instances (Cases 12 and 13) the destruction of the aortic valve caused a hernia-like protrusion into the adjacent auricular cavity, and a rupture of the protrusion had occurred in Case 13. The figures (Plates 9 and 10) show some of these features, which, taking the series as a whole, were most impressive.
4. Of the 20 cases, in five there was evidence of pre-existing valvular abnormality, which agrees well with the recorded experience. Four cases showed old rheumatic thickening, the other (Case 8) a congenital bicuspid aortic valve.
5. Evidence of embolism was found in eight cases at autopsy. The collected figures from the literature indicate that embolic phenomena are likely to occur in approximately 50 per cent. of cases.
6. A striking feature is the frequency of generalized pneumococcal infection, shown by meningitis, empyema, pericarditis, and peritonitis, at least one of these being present in most cases.
7. In seven cases the mitral valve alone was affected, in nine the aortic alone,

in three both aortic and mitral, and in one there were vegetations on both mitral and tricuspid valves; that is, in 16 out of 20 cases one valve only was involved and only once did the disease occur on the right side of the heart.

The high incidence of the disease on the left side of the heart is shown in Table II, and our figures agree with those of other authors. It is of interest to note that, compared with other forms of infective endocarditis, the bicuspid valve is frequently affected (Preble, 1904; Lord, 1932; Locke, 1924).

TABLE II

Valves Affected in Pneumococcal Endocarditis

Valves affected	Preble (1904)	Thayer (1926)	Lord (1932)	Ruegsegger (1938)	Present series
Aortic only	56	9	7	7	9
Mitral only	40	3	8	4	7
Aortic and mitral	20	7	3	2	3
Tricuspid only	12	2	2	1	—
Pulmonary only	5	1	—	—	—
Aortic, mitral, and tricuspid	5	3	2	—	—
Mitral and tricuspid	2	—	—	—	1
Aortic and tricuspid	1	1	—	1	—
Tricuspid and pulmonary	—	—	1	—	—
Totals	141	26	23	15	20

In six cases vegetations were examined microscopically. They showed the usual structure of a deep layer of granulation tissue at the periphery of the base, a mass of organisms and polymorphonuclear leucocytes in the centre of the base, and a thick layer of fibrin forming the main bulk. Generally the smooth surface was formed by a condensed layer of fibrin, which was occasionally lined by a few flattened fibroblasts, but there was no evidence of any endothelial covering.

Clinical Features

Incidence. It is difficult to obtain a true account of the incidence of this disease as there is a great discrepancy between the clinical and autopsy figures, but it is evident that the condition must be much more common than is generally supposed. Preble (1904) collected from the literature a series of 11,243 cases of pneumonia of which 126 (1 per cent.) were considered to have pneumococcal endocarditis, while in 1,775 autopsies on patients with pneumonia 86 (4 per cent.) showed endocarditis. He concluded that the condition is present in approximately 1 per cent. of all cases and 4 per cent. of the fatal cases. Lord (1932) gives details of 337 cases of pneumonia coming to autopsy at the Massachusetts General Hospital and in 14 (4 per cent.) there was evidence of acute endocarditis. A more recent survey by Ruegsegger (1938) gives a higher incidence. In his series of 655 cases of pneumonia, endocarditis developed in 3 per cent. and was found in 15 per cent. of 214 cases which came to autopsy. It is of interest that Osler (1885) found pneumococcal endocarditis in 16 per cent. of 103 similar

autopsies. It is perhaps important to note that these reviews are American and that pneumococcal infections in the coloured races are usually severe. Thayer (1926) considers that race may be a factor in the incidence of pneumococcal endocarditis, but Ruegsegger (1938) finds no significant difference in the incidence in white and negro patients. Our own experience at Crumpsall Hospital is shown in Table III.

TABLE III

Incidence of Pneumococcal Endocarditis in Autopsies on Cases of Lobar Pneumonia at Crumpsall Hospital

Year	1935	1936	1937	1938	1939	1940	1941	1942 (to May 31st)	Total
Autopsies on pneumonia cases	20	18	10	7	30	31	43	16	175
Acute bacterial endocarditis	5	2	0	1	3	4	2	2	19

The Annual Reports of the Medical Officer of Health of Manchester state that during the period covered by Table III, 2,185 cases of lobar pneumonia were treated in Crumpsall Hospital with 582 deaths, but since these figures include terminal and post-operative cases and many in which the diagnosis was open to doubt, it is not felt that any definite statement can be made from personal observation concerning the true incidence of the disease. The condition was present in 9 per cent. of all cases examined *post-mortem*.

Sulphapyridine therapy was started late in 1938 and as the authors were engaged on a study of the effects of this drug in lobar pneumonia there has been an increase in the number of autopsies on these cases, but there was no increase in the proportion of such cases showing pneumococcal endocarditis. There is no evidence that sulphapyridine has increased the true incidence of the disease; the figures in this series suggest rather the contrary.

Sex. The disease is more frequent in male than female subjects. In Preble's (1904) series 69 per cent. of 132 were male; of the 20 patients here described 15 were male. This is in keeping with the greater number of male patients admitted to hospital with pneumonia.

Age. All observers agree that the disease is more frequent during middle life than at any other period. About three-fifths of all pneumonias occur during the first three decades, but only one-fifth of the cases of pneumococcal endocarditis are found amongst patients of this age. This curious age relationship is well shown in the patients here considered, for 15 of the 19 were between 35 and 55 years of age, and of these, 11 were in the forties.

Mode of onset. The early symptoms of endocarditis are often unrecognized during the acute stage of pneumonia. The prolongation of the symptoms of severe infection after the eighth or ninth day or their recurrence after a short apyrexial interval, lead one to suspect a complication. Recrudescence of pneumonia is a common diagnosis under such conditions, and should this prove fatal and no autopsy be performed, it is easy for the true diagnosis to be missed. In a proportion of cases, seven out of nine in the present series,

after the natural subsidence of pneumonia symptoms, there is a quiescent period lasting from a few hours up to 12 days during which the temperature and respirations are normal and the patient seems to be on the road to recovery. This afebrile period is usually less than five days in duration. Symptoms suggesting a re-infection then develop, and lead within a few days to those of a pneumococcal septicaemia which proves fatal. It is unusual for the pulse-rate to return to normal during the afebrile period. Since sulphapyridine treatment was instituted, there have been no opportunities to observe this apyrexial interval which may be part of the clinical syndrome.

Clinical features of the developed disease. The temperature is high, usually intermittent, and associated with severe sweating. Rigors are fairly common, particularly during the sharply peaked pyrexia of the terminal few days. The pulse-rate is raised out of proportion to the temperature. Bradyardia is rarely found, either in cases complicated by or without meningitis.

Embolism. Skin petechiae are noted in the minority of patients. They seem more liable to develop as a late feature of the disease. It is probable that they are frequently overlooked, as they are not usually sought for in these febrile and dangerously ill patients unless the diagnosis of pneumococcal endocarditis is considered. Petechiae were found in three of seven patients in whom careful search was repeatedly made. They were larger than those usually found in subacute bacterial endocarditis, and some showed a central white spot. This type of petechial eruption is supposed to be indicative of some form of bacterial endocarditis, but this is by no means true. We have seen it in other conditions, notably in the febrile stage of acute leukaemia and in pernicious anaemia. The longer the duration of the disease, the more prone is the patient to embolism involving a large artery, a natural result of the increasing size of the vegetations and of softening at their bases. This may result in hemiplegia, perisplenitis, haemoptysis, or haematuria. Embolism of a large vessel is infrequent, at least not in the situations which give rise to obvious clinical signs or symptoms. In four cases only in this series did it occur; in one (Case 6) a left hemiplegia developed on the fifty-fifth day of the illness, and in another (Case 14) in which signs of right hemiplegia occurred on the thirty-sixth day, a cerebral abscess was found at autopsy.

The spleen is rarely enlarged sufficiently to be palpable. Thayer (1926) stated that in his patients the spleen could be felt in only 10 per cent. In only two of the 19 adult patients in our series was the spleen palpable, but in 11 it was found to be enlarged at autopsy. It is of interest that the spleen could be felt easily in the child with pneumococcal endocarditis.

Clubbing of the fingers is uncommon, owing, no doubt, to the short duration of the illness. It may be found in patients who survive for a few weeks, since the nature of the disease, a septic lesion involving heart and lungs, is such as to produce clubbing in the minimum of time (Lord, 1932).

Conditions associated with pneumococcal septicaemia. Pneumococcal meningitis occurred in at least nine of our 20 patients. In a desperately ill patient

the meningitic symptoms may well pass unrecognized unless this complication be remembered. Screaming attacks and coma during the last few days of the illness strongly suggest its presence. In the earlier cases, there is no clinical record of meningitic symptoms, and the autopsy did not include examination of the brain. In six cases clinical evidence of meningitis was confirmed at autopsy, while in another the diagnosis was substantiated by lumbar puncture; in yet another case there was unconfirmed clinical evidence of meningitis. In Ruegsegger's (1938) series meningitis developed in all but one of 19 cases.

Pericarditis. Pericardial involvement is frequent. Half of Loekke's (1924) patients showed acute pericardial lesions. Pneumococcal pericarditis may be fibrinous, but is usually purulent. Its occurrence may draw attention to the heart during the acute illness and should always lead one to suspect that the endocardium as well as the pericardium may be infected. Pericardial friction is apt to mask the cardiac murmurs, and so may cause delay in the correct diagnosis; Case 7 illustrates this point. It is easy to make a mistake in the other direction, and, having diagnosed acute infective endocarditis, to fail to detect the signs of acute pericarditis. Indeed, the signs of a purulent pericarditis may be extremely elusive. On at least two occasions during recent months we have failed to detect any sign of pericarditis in patients who at autopsy had an ounce or more of pus in the pericardial sac. In Case 12, for example, where at autopsy an ounce of thin green pus was found in the pericardial sac in addition to typical vegetations on the aortic valve, acute pneumococcal endocarditis was diagnosed during life, but the coexisting pericarditis was missed.

Arthritis, according to Thayer (1926), occurs in one-third of all cases. Usually one only of the larger joints is involved, leading in half of the cases to pus within the joint. Only one of our cases had this complication.

Peritonitis. Although not often described in association with pneumococcal endocarditis, peritonitis was present in one patient (Case 3) of the present series. It is noteworthy that this patient was pregnant.

Empyema. This complication occurred in eight out of the 19 patients whose primary illness was pneumonia.

Signs in the heart. Cardiac examination does not always, for various reasons, settle the diagnosis. Auscultation of the heart is by no means easy in patients who are so acutely ill. Frequent and noisy respirations and pulmonary adventitious sounds may easily overwhelm the faint murmurs which develop in the rapidly beating heart. The condition of the heart before the onset of pneumonia is usually unknown, and murmurs due to chronic valvular disease may not be detected at the first examination. A murmur heard during the afebrile period may be attributed to other causes unless the possibility of pneumococcal endocarditis is borne in mind. Again, pericardial friction sounds can make the interpretation of the findings on auscultation very difficult. Most systolic murmurs which develop during an attack of acute pneumonia are not due to endocarditis. Lastly, some

eases show no auscultatory evidence of endocarditis. This point is illustrated by Case 14, in which the presence of pneumococcal endocarditis was strongly suspected for some weeks before the patient died, though careful examination of the heart failed to reveal positive evidence. We are convinced, however, that if a diastolic murmur is known to have developed during an attack of pneumonia, the patient is suffering from infective endocarditis. It is of interest that in Case 14, in which there was gross obstruction of the mitral orifice by a large mass of vegetation (Plate 9, Fig. 2) making it difficult to understand how the blood forced a passage into the ventricle, there was no prestolic mitral murmur.

A systolic murmur can be regarded as significant only if it is associated with general signs of septicaemia, if it is localized, and if it tends to become louder as the disease progresses. The importance of careful examination of the heart and blood-pressure at the commencement of the pneumonia is obvious, and particular attention should be paid to the aortic second sound in patients of middle age. Since it is common for a normal aortic valve to be involved, a progressive fall in the diastolic blood-pressure may be a sign of great value. It may happen that acute pneumococcal endocarditis is implanted on an old rheumatic lesion already causing aortic incompetence. In this case changes in the aortic diastolic murmur may be difficult to assess, but a falling diastolic blood-pressure provides valuable evidence of the superadded infection. Both Preble (1904) and Rueggsegger (1938) emphasize the importance of signs of aortic incompetence. In Case 13 there was a rapid fall in the diastolic blood-pressure, from 55 mm. to 10 mm. within 10 days. Congestive heart failure occurs as a terminal feature in the minority of patients; it is recorded in three of our 20 cases.

Blood changes. Blood-cultures are nearly always positive, and the growth of pneumococci is usually heavy. Some leucocytosis is the rule, and occasionally it is pronounced, but the leucocyte count may be only slightly raised even during the florid stage of the disease. Progressive anaemia is not a usual feature, but was present in the child in the present series.

Treatment

So far as we know, once the disease is established, the issue is invariably fatal. Type-specific serum and sulphapyridine have some symptomatic influence but cannot cure the disease. As with subacute bacterial endocarditis, measures taken to render the blood-stream sterile or to increase the general body resistance seem to have very little influence on the valvular lesions. Specific treatment may cause considerable reduction in pyrexia and rigors with a lesser effect on the pulse-rate, and since the high fever causes profound discomfort, sweating, and malaise, the patients are thereby relieved. The blood-culture is usually, but not invariably, rendered sterile within a few hours of the administration of sulphapyridine, but pyrexia, rigors, and bacteraemia recur within 24 hours when it is stopped. Such

effects can be produced repeatedly, as in Case 14. Twelve blood-cultures were taken when patients were not under the influence of sulphapyridine, and of these 10 were positive; seven blood-cultures were taken whilst the patients were taking sulphapyridine, and two were positive.

Prevention

Prevention therefore seems to afford the main hope of success. Much depends on the actual time at which the endocardium is first involved. It is probable that this sometimes occurs during the early days of the acute pneumonic process, particularly in patients with previous endocardial damage, or in whom resistance to blood-stream invasion is poor (as in Cases 3, 8, and 10). In such patients prophylaxis is difficult. It seems highly desirable that all patients known to have valvular disease of the heart or congenital heart disease, and patients with a sluggish general reaction to a pneumonic infection (manifested by clinical signs, poor leucocytosis, and persistence of a positive blood-culture for more than 24 hours) should have antipneumococcal type-specific serum in addition to full doses of sulphapyridine. We have given some indication of the value of combining sulphapyridine with type-specific serum in patients with a positive blood-culture in work previously reported (Don, Luxton, Donald, Ramsay, Macartney, Smith, and Adderley, 1940). Sixteen pneumonia patients with bacteraemia were treated with sulphapyridine alone, with four deaths; 10 bacteraemic patients, all over 60 years of age, were treated with sulphapyridine and serum, without a death. Another possible means of prevention is more careful observation of patients after treatment with sulphapyridine. 'Secondary pyrexia' may be due to empyema, the prompt diagnosis and treatment of which may possibly prevent the onset of endocarditis, since a pneumococcal empyema may be a reservoir from which organisms are brought to the endocardium. The fact that patients are having sulphapyridine does not negative this possibility, since pneumococci are protected by pus against its action and pneumococci can easily be cultured from empyema pus containing a high concentration of sulphapyridine (*Proc. Roy. Soc. Med.*, 1939). 'Masked' empyema, in which the development of pus in the pleural cavity is not accompanied by the usual degree of pyrexia and constitutional disturbance, is not uncommon since sulphapyridine came into general use, so that it seems important to watch for this complication and undertake its prompt treatment. The question of the time at which drainage of a pneumococcal empyema should be undertaken is naturally raised. It is uncommon for pneumococcal empyemas to be drained too early, and it is more common for drainage to be established too late. We suggest that in pneumonia cases treated with sulphapyridine the appearance and fluidity of the pus are not decisive criteria. If the fluid in the chest contains pneumococci and many polymorphonuclear cells, and the active pneumonic process is at an end (the latter point is usually not difficult to assess clinically), then drainage should be considered without waiting for the pus to become 'creamy'.

Illustrative Case Reports

Case 8. A man aged 43 years was admitted to hospital on the fourth day of an illness which was not definitely diagnosed as lobar pneumonia until the eleventh day. A left-sided empyema was found on the twenty-fourth day. This was followed within twenty-four hours by the appearance of a very soft diastolic bruit down the left border of the sternum and by oedema of the feet. The bruit became more pronounced and the blood-pressure was 145/65 mm. Petechiae, few in number and larger than those commonly met with in subacute bacterial endocarditis, some with a central white spot, were found in the right axillary region on the day before death, at which time blood-cultures gave a growth of more than 1,000 colonies per c.c. of a pneumococcus Type 5.

The autopsy showed pneumonic consolidation of both lobes of the left lung with thick pus in the costophrenic angle. The heart was not enlarged (weight 340 gm.) and the pericardial sac contained approximately 120 c.c. of thin serous fluid. The mitral, tricuspid, and pulmonary valves were normal. The aortic valve was bicuspid, the cusps being almost exactly equal in size, situated anteriorly and posteriorly, with the commissures left and right. There was no indication of subdivision in either cusp. The coronary orifices were both situated nearer the right commissure than the left. Both cusps had clearly defined margins except at the right commissure where there was a polypoid mass of greenish-yellow vegetation attached to the ventricular and aortic surfaces of both cusps.

Thin pus was present over the whole surface of the brain.

Type 5 pneumococcus was isolated from cultures taken from the vegetations.

This is an unusual case in that acute pneumococcal endocarditis attacked a congenitally bicuspid aortic valve, which, although prone to infections with the streptococcus viridans, is rarely infected by other organisms. Other features noted in several cases are the gradual onset, the late occurrence of petechiae, and the absence of splenic enlargement.

Case 10. A man aged 23 years was admitted to hospital on the fourth day of typical lobar pneumonia affecting the right upper lobe. The sputum contained Type 2 pneumococci, and blood-cultures taken on each of the four days after admission gave a heavy growth of this organism. The patient was acutely ill throughout. On the fifteenth day he was unable to speak and the right plantar response was extensor. The cerebrospinal fluid was frankly purulent and yielded a growth of Type 2 pneumococcus. The heart was examined daily, but no abnormal physical signs were detected.

This patient was a control case in a series of 234 cases of lobar pneumonia, some treated with sulphapyridine alone, some with sulphapyridine plus type-specific serum, and some acting as controls receiving neither treatment (Don, Luxton, Donald, Ramsay, Macartney, Smith, and Adderley, 1940). He was therefore not treated with sulphapyridine until very late and died within a few hours of its commencement. There is no record of petechiae, splenic enlargement, or positive clinical indications of infective endocarditis.

At autopsy there was grey hepatization of the upper and middle lobes and the upper half of the lower lobe of the right lung, and extensive purulent meningitis. The spleen (283 gm.) was moderately enlarged, dark grey, and soft. The pericardial sac contained approximately 60 c.c. of straw-coloured fluid. There were many small, soft, friable vegetations along the line of contact of both mitral cusps, and a small vegetation in the centre of each

aortic cusp at the point of contact. There was no evidence of pre-existing valvular disease.

Case 12. A woman aged 54 years had typical lobar pneumonia affecting the right lower lobe, and on admission pneumococcus Type 19 was isolated from the sputum and the blood. Improvement followed large doses of sulphapyridine, but the pulse was rarely below 90 and on the eighteenth day there was a recrudescence of symptoms with signs of extensive consolidation in the right lower lobe. The sputum still contained Type 19 pneumococci, but the blood-culture was negative. Oedema of the feet and sacrum was then observed. Further doses of sulphapyridine reduced the temperature, but the pulse-rate was still over 100. On the twenty-fourth day 270 c.c. of thin green pus containing the same type of pneumococcus were aspirated from the right base and three days later rib resection with drainage was performed. On the thirty-first day a final course of 39 gm. of sulphapyridine was started and from the thirty-first day until her death, 11 days later, the patient was acutely ill with sweating, dyspnoea, cyanosis, and a rapid pulse. Infective endocarditis was diagnosed six days before death.

To-and-fro aortic bruits were present, the systolic element being coarse, but without any thrill. The blood-pressure was 130/50 mm. and although the ventricular rate was only 90 per minute, the rhythm was completely irregular, suggesting auricular fibrillation. Oedema of the legs was marked. No petechiae, clubbing of fingers, or 'splintering' under the finger nails was observed, and the spleen was not palpable. The patient was delirious, and although no definite neck rigidity was elicited, both plantar responses were extensor and on clinical grounds we were strongly of opinion that she had meningitis. She was unfit for lumbar puncture and it is unfortunate that at the subsequent autopsy permission to examine the brain was refused.

Autopsy confirmed the presence of a small encysted empyema compressing the lower lobe of the right lung which was semi-consolidated and friable. The heart weighed 368 gm. The pericardial sac contained approximately 30 c.c. of thin greenish pus, and several petechial haemorrhages were present on the visceral surface of the epicardium. On the mitral cusp of the aortic valve there was a polypoid mass of vegetation occupying practically the whole length of the cusp to a maximum depth of 1.5 cm. The surface of the vegetation was smooth, but there was ulceration at the base of the cusp beneath the vegetation, and this had resulted in a small bulge which showed in the left auricle just above the base of the aortic cusp of the mitral valve. There was no evidence of old endocarditis. The spleen (340 gm.) was enlarged, dark, and firm, and the liver showed a moderate degree of multilobular cirrhosis.

This case shows several interesting features which are discussed in the text.

Case 20. A male child aged 13 months was admitted to Booth Hall Hospital for Sick Children on 14th July, 1940, with a seven days history of vague illness suggesting mastoiditis. Clinical examination showed nothing but coryza with a temperature of 99° F., and sulphapyridine was given in four-hourly doses of 0.25 gm. to a total of 3.75 gm. The pyrexia was controlled for twenty-four hours, but thereafter returned and did not respond to double the above dosage of sulphapyridine. On 23rd July cyanosis and an apical systolic murmur were noted, but there was no clinical or radiographic evidence of pneumonic consolidation. Two days later the spleen was palpable. The systolic murmur became more definite and a blood-count at

this time showed red cells 2,400,000 per c.mm., haemoglobin 40 per cent., and white cells 22,400 per c.mm. The bruit became audible over the whole praecordium and the pallor and general deterioration increased until death on 30th July.

Endocarditis was suspected, but no blood-cultures were taken.

The following were the chief features of the autopsy which was performed seven hours after death.

The body was well nourished and of normal size. The skin and mucous membranes were pale and a few small petechiae were present in the skin of the forearms.

In the heart the ductus arteriosus and the foramen ovale were closed. The mitral orifice as seen from the auricular side was almost occluded by a yellowish, polypoid mass measuring approximately 1.4×1.0 cm. attached to the aortic cusp of the mitral valve which was ulcerated in the centre beneath the vegetation. Although the vegetation was friable and easily detached the surface was smooth. There was no evidence of previous damage to the valves.

In the lungs there were many petechial haemorrhages beneath the visceral pleura, and there were extensive areas of atelectasis with compensatory emphysema.

The spleen (40 gm.) was firm, but not enlarged.

The liver (370 gm.) was pale and yellowish.

The kidneys (each 25 gm.) showed several small petechiae on their convex surfaces.

In the meninges over the cortex several small haemorrhages were present. Pus was present in the right mastoid air cells. Cultures from the vegetations gave a pure growth of pneumococcus Type 8, but this organism was not recovered from the mastoid.

Bacterial endocarditis in infancy and very early childhood is rare and in the English literature we have been able to find only two cases in patients younger than this (Dible, 1919; D'Ewart, 1931). The mastoid might be considered as a possible source of the infection, but this is unlikely, since pneumococci were not isolated from it and pus in the middle ear is a fairly frequent finding in autopsies on young children.

Case 14. A man aged 43 years came into hospital on the seventeenth day of an illness diagnosed as subacute rheumatism. He had pain in the right knee referred from the right hip which showed acute arthritis. There were signs of fluid in the right pleural cavity. Five days later a pint of thin green pus containing Type 1 pneumococci was aspirated from the chest, and aspiration was repeated on three subsequent occasions as the pus was then considered to be too thin for rib-resection; subsequently this operation was carried out on the thirty-first day. On the thirty-sixth day there was fever and a rigor, followed by further rigors, sweating, and delirium. A right hemiparesis was then observed, with right hemianæsthesia, right homonymous hemianopia, and sensory aphasia, diagnosed as being due to a metastatic abscess in the left temporal lobe. This necessitated a second course of sulphapyridine and the administration of 135,000 units of type-specific serum, with definite improvement of the cerebral signs. When the sulphapyridine was stopped, daily rigors occurred and the blood-cultures were positive; with further doses of the drug the temperature immediately returned to normal, the pulse-rate fell, and no rigors occurred until this treatment was again omitted.

On the fifty-fourth day the question of pneumococcal endocarditis was carefully considered. The heart was regular and not enlarged, a soft, fairly localized, systolic bruit was present at the apex and between the apex and the sternum, and the mitral second sound was audible though rather soft, but no aortic murmurs were heard. The blood-pressure was 110/60 mm. No oedema or clubbing was found. No petechiae were found in skin, conjunctivae, nails, or mouth. The spleen was not palpable and there was no sweating. The retinae were normal. The conclusion reached was that although there was no positive evidence of pneumococcal endocarditis, it was possible that there were vegetations on the mitral valve.

The patient lived for another 17 days, having intermittent pyrexia but no rigors. The leucocyte count tended to fall. On the seventy-first day the patient suddenly became unconscious, with sweating and a weak pulse. Rupture of a cerebral abscess into a ventricle was diagnosed, and 3 c.c. of soluble sulphapyridine were given intravenously and then 3 c.c. intramuscularly every four hours. The patient died 12 hours later.

Autopsy. There were a few flakes of pus in the right hip joint and the lining of the joint was haemorrhagic.

The heart (285 gm.) showed right-sided dilatation. Attached to the aortic cusp of the mitral valve and appearing to fill completely the mitral orifice was a large, buff-coloured, polypoid mass approximately 2.5 cm. in length and 1.0 cm. in depth. The vegetation was ovoid in shape and had a smooth surface. The destructive process had extended completely through the substance of the cusp, but the perforation was completely covered by the mass of vegetation.

In the lungs and pleurae there was a small localized collection of pus in the sulcus between the middle and lower lobes, but no free pus and no evidence of lung consolidation; the left side was normal.

The liver (1,984 gm.) showed moderate 'nutmeg' mottling.

The spleen (227 gm.) was enlarged, dark, and fairly firm; many contracted and several recent infarcts were present.

The kidneys (right 170 gm., left 200 gm.) each contained two small, soft, yellow infarcts.

In the brain practically the whole of the left occipital lobe was occupied by an abscess cavity with soft, ragged walls. The abscess flanked the posterior horn of the lateral ventricle and had ruptured into it. The surface of the brain was flattened and coated with a thin layer of pus.

This instructive case illustrates the following points:

1. It may be almost impossible to diagnose pneumococcal endocarditis in the absence of embolic phenomena, but this diagnosis is probable when any embolic lesion occurs in a case of lobar pneumonia.

2. Cardiac signs may be quite indecisive. An enormous vegetation may be present on the mitral valve without producing a murmur.

3. Sulphapyridine lowered the temperature and temporarily checked the bacteraemia, but within twenty-four hours of its cessation both recurred.

4. Type-specific serum and sulphapyridine together failed to arrest the condition.

5. The fact that the empyema pus was thin and that the patient's general condition was fair led to a delay in drainage.

TABLE IV. Summary of Findings in 20 Cases of Pneumococcal Endocarditis

Case No.	Age	Sex	Duration of illness (days)	Valves involved	Previous valvular lesion	Site of pneumonia	Pneumo-coccus type	Splenic enlargement	Leucocytes (maximum) per c.m.	Empyema	Pericarditis	Blood-cultures	Spleen	Non-specific	Treatment
1	43	F.	30	Mitral	Old mitral thickening	R.U.L.	—	+	25,600	0	0	—	Infarcts	"	
2	47	M.	18	Aortic and mitral	0	R.L.L.	—	+	14,600	0	0	—	Spleen and kidneys	"	
3	21	F.	15	Aortic and mitral	Chronic rheumatic thickening of aortic and mitral	R.U.L.	—	—	—	+	+	—	0	"	
4	47	M.	31	Aortic	0	R.L.L.	—	—	—	—	+	—	0	"	
5	32	M.	16	Aortic	Old rheumatic disease of aortic and mitral	L.L.L.	—	—	—	—	—	—	0	"	
6	41	M.	61	Aortic	0	R.L.L.	—	+	—	0	0	—	0	"	
7	41	M.	20	Mitral	0	R.L.L.	1	0	16,000	0	0	—	Kidneys	"	
8	43	M.	27	Aortic	0	R.U.L.	—	0	18,200	0	0	+	Brain	"	
9	46	M.	10	Mitral	Congenital bicuspid aortic valve	L.U.L.	5	0	22,000	+	0	+	Spleen	"	
10	23	M.	15	Aortic and mitral	Old mitral endocarditis	R.U.L.	3	+	16,100	0	0	+	0	"	
11	59	F.	17	Mitral	0	L.L.L.	2	+	15,400	0	0	—	—	"	
12	51	F.	44	Aortic	0	R.U.L.	—	0	10,600	+	0	+	0	"	Sulphapyridine 8 gm.
13	36	M.	33	Aortic	0	R.L.L.	19	+	40,000	+	+	—	0	"	Sulphapyridine 48 gm.
14	43	M.	71	Mitral	0	R.L.L.	1	+	25,000	+	0	+	0	"	Sulphapyridine 105 gm. Drainage of empyema
15	52	M.	33	Mitral	0	R.L.L.	1	+	20,500	+	0	+	0	"	Sulphapyridine 105 gm. Specific serum. Drainage of empyema
16	67	M.	50	Mitral and tricuspid	0	R.U.L.	—	+	13,000	0	0	+	Spleen, kidneys, and brain	"	Sulphapyridine 132 gm. Drainage of empyema
17	42	M.	31	Aortic	0	L.L.L.	1	0	—	0	0	0	Liver and spleen	"	Sulphapyridine 13 gm.
18	52	F.	32	Aortic	0	L.L.L.	1	+	15,200	+	0	+	0	"	Sulphapyridine 8 gm.
19	56	M.	44	Aortic	0	R.U.L.	1	+	20,000	0	0	+	0	"	Sulphapyridine 56 gm.
20	13 mths.	M.	23	Mitral	0	R.L.L.	1	0	18,000	+	+	repeatedly	0	"	Sulphapyridine 26 gm. Sulphamethazine 108 gm.
						—	8	—	22,400	0	0	+	Spleen	"	Sulphamethazine 126 gm. Sulphapyridine previously at home
												repeatedly	0	"	Sulphapyridine 31 gm.

Summary and Conclusions

A study has been made of 20 cases of pneumococcal endocarditis, and from the clinical and post-mortem data and a review of the literature, the following observations were made.

1. Pneumococcal endocarditis is a condition usually, but not invariably, associated with pneumonia, and is found in from 5 to 15 per cent. of cases of pneumonia coming to autopsy.
2. It can occur at any age, but is most common in middle life.
3. A case of pneumococcal endocarditis in a child of thirteen months is described. Few cases at so early an age have been reported.
4. The left side of the heart is more prone to infection than the right side, and the aortic valve appears to be specially vulnerable to the pneumococcus.
5. The lesions on the heart valves are so typical as to be almost diagnostic.
6. Previous damage to the heart valves appears to have a predisposing effect. Syphilitic aortitis is rarely a factor. One case here described showed a congenital bicuspid aortic valve.
7. It is suggested that the clinical picture is fairly characteristic and the special features of value in diagnosis are discussed.
8. Petechiae and embolism are found in a minority of cases and are usually a terminal feature.
9. The spleen is not usually palpable, though *post mortem* it was found to be enlarged in 10 of our cases. Clubbing of the fingers is not often found, owing to the brevity of the illness.
10. Signs of generalized pneumococcal infection, especially meningitis, are common.
11. Pericarditis developing during or after acute pneumonia should always lead to the suspicion that the endocardium may be infected.
12. Examination of the heart does not always settle the diagnosis, but if a diastolic murmur is known to have developed during an attack of acute pneumonia it is highly probable that infective endocarditis is present. The aortic second sound and diastolic blood-pressure demand particular attention in middle-aged patients with pneumonia.
13. Eight of our 20 patients had empyemas, and it is suggested that any factor delaying the diagnosis and early drainage of an empyema may predispose to pneumococcal endocarditis. The effect of sulphapyridine in this connexion is considered.
14. Treatment of the developed disease with sulphapyridine and serum produces symptomatic improvement, but has no effect on the ultimate result; prevention is the chief aim of treatment.

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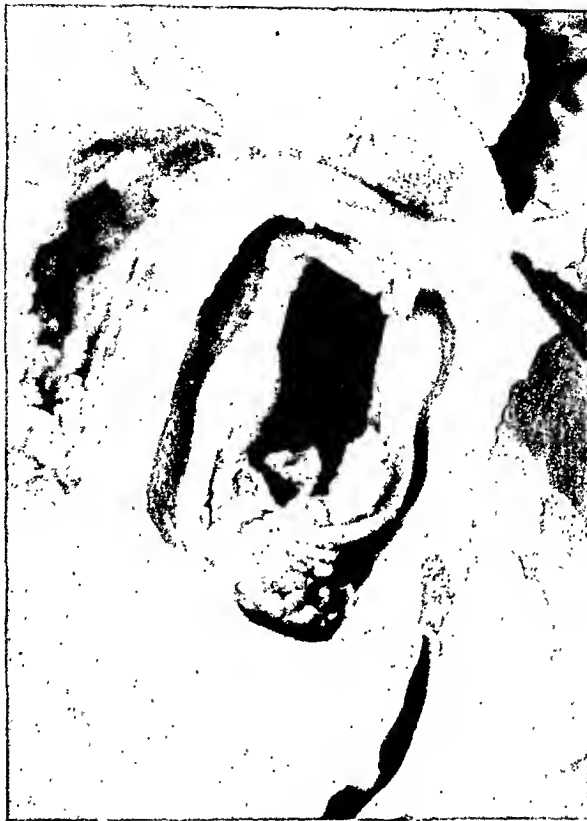


FIG. 1. Case 8. A bicuspid aortic valve with pneumococcal vegetations

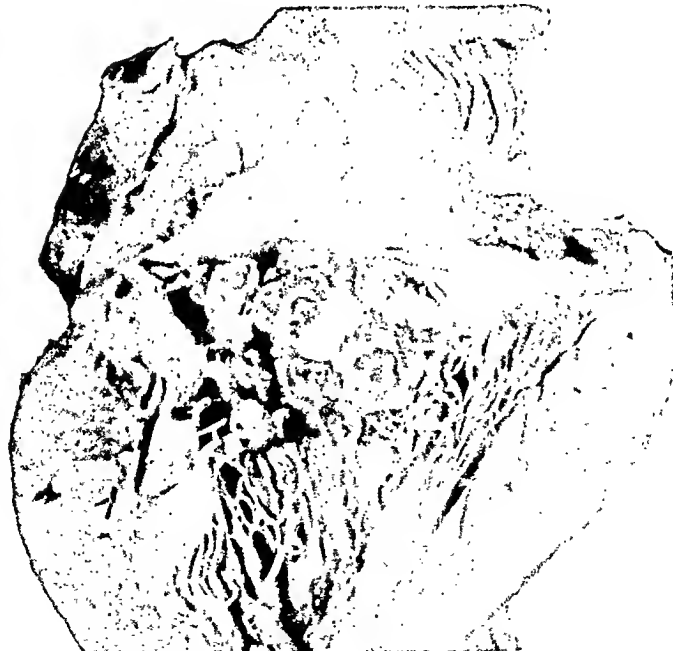


FIG. 2. Case 14. Bulky polypoid pneumococcal vegetations on the mitral valve



FIG. 3. Case 19. Polypoid type of pneumococcal vegetation on the aortic valve

A CONTRIBUTION TO THE STUDY OF MELORHEOSTOSIS: UNUSUAL BONE CHANGES ASSOCIATED WITH TUBEROSE SCLEROSIS¹

By G. S. HALL

(The Birmingham United Hospital)

With Plates 11 to 14

Introduction

FOR more than two centuries the problem of osteogenesis has held the attention of anatomists and surgeons, and the history of the various advances by which present-day views have been reached makes fascinating reading. With the advent of radiography, the study of bone received great impetus, and many new disorders, some still of unknown pathology, were described. I have had the good fortune recently to be able to investigate one such disorder, the pathology of which is interesting and, so far as I know, has not been described previously. Through the kindness of Dr. A. P. Thomson, I was able to keep under observation for a number of years a boy suffering from tuberose sclerosis with unusual bony lesions of the right hand (Hall, 1940). This boy, whom I demonstrated at the Birmingham Meeting of the Association of Physicians in 1939, died eventually from the effects of raised intracranial pressure. I was able to secure a post-mortem examination, the result of which seems to throw further light on the function of the periosteum in relation to the formation and growth of bone, and on that little-known disorder which Léri and Joanny (1922) described and named melorheostosis. I propose to review our knowledge of this condition, to recall the chief features of my case, and to describe and discuss the pathological findings.

In 1922 Léri and Joanny described a unique disorder of bone consisting of a 'flowing' hyperostosis affecting the left upper extremity of a 39-year-old woman. For nearly 30 years the patient had noticed a deformity of the left hand consisting of a divergence of the index and middle fingers, and for 22 years, after a fall on the left elbow, had been unable to extend that forearm fully; her only other symptom had been some discomfort in the corresponding shoulder for eight years. On examination there was a striking hypertrophy and deformity of the affected fingers which were enormous and bossed, and diverged from one another at the second phalanx; the deformity resembled that seen in certain congenital macrodactyls and multiple chondromas.

¹ Received August 14, 1942.

Other noticeable features were the tightness and slight tenderness of the skin of these fingers, the presence of an elongated ridge on the back of the hand over the second and third metacarpal bones, considerable limitation of movement of the affected fingers, wrist, elbow, and shoulder, and the presence of an irregular palpable thickening of the humerus and coracoid process. X-ray examination revealed a curious hyperostosis involving the whole length of the affected limb, but confined to certain bones and certain parts of the bones of that limb alone. Those affected were the glenoid cavity and coracoid process of the scapula, the humerus, the proximal half of the radius, the distal two-thirds of the ulna, certain carpal bones, and the radial halves of the second and third metacarpals and their phalanges. The hyperostosis was dense and irregular, affected only one aspect of the bones, and because of its resemblance to the guttering of a candle, Léry and Joanny gave to the condition the name of melorheostosis. They noted that the lesions did not correspond to any vascular or nervous distribution and concluded that the condition was probably of developmental origin.

Lewin and MacLeod (1925) recorded the case of a 35-year-old man with osteosclerosis in the ulnar region of a forearm and hand. The fourth and fifth fingers of the right hand had been swollen since the age of six years and within a short time the ulnar region of the forearm had become thickened and outwardly curved. Since the age of 10 years he had had intermittent pain in the limb, which had become increasingly deformed and restricted in movement. On examination, the affected forearm was curved outwards, the skin over the corresponding part of the hand was red, indurated, and tender, while the fourth and fifth fingers were swollen and bent. On the inner side of the ring finger there were two knob-like excrescences similar to those seen in gout, while several bony masses could be felt attached to the proximal part of the ulna. X-ray examination revealed hyperostosis, eburnation, and sclerosis of the ulna, the contiguous carpal bones, and the fourth and fifth metacarpals and their phalanges.

Putti (1927) described two cases of what he called osteitis eburnisans monomelica, a term which he preferred to the name given to the disorder by Léry and Joanny. His first case, details of which had been described by Muzii in 1926, was that of a 10-year-old girl with involvement of the left lower limb. The left knee had been swollen for five years and radiologically there were extensive areas of dense bone, extending in an interrupted linear manner from the left side of the pelvis down to the big toe of the left foot; there was also an associated craniostenosis. His second case was that of an eight-year-old girl, also with involvement of the left lower limb. A deformity of the foot consisting of pes valgus had been present during infancy, and for one year the child had complained of pain in the limb. There was considerable limitation of movement of the affected hip, and in addition to the deformity of the foot marked genu valgum. Radiological changes resembling, but less marked than, those of the first case extended from the acetabular region into the foot. An osteotomy of the knee was performed. Putti found

histological evidence of considerable perivascular formation of new bone around vessels which seemed more numerous than normal, though some of them were occluded. The bony lamellae were distributed regularly, and in some areas degenerative changes were present. He regarded the perivascular formation of new bone, the distribution of which he attributed to the longitudinal course of the nutrient artery, as the cause of these degenerative changes. He therefore postulated a functional disturbance—of unknown cause, but probably congenital—of the sympathetic vasomotor control of the affected part, resulting in the proliferation of an unusually dense bone. These views were upheld later by Lazzarini (1928). Policard's views of the sections were that the degenerative changes were primary and that the formation of dense new bone was of secondary importance.

Zimmer (1927) described the case of a 32-year-old man who had had pains in both lower limbs for 11 years. Radiologically, there was evidence of an intermittent dense hyperostosis involving the left lower limb from the ilium to the foot where the dorsum of the fourth toe was thickened and covered by a tense shiny skin; the tibia was almost unaffected. He gave the name of *osteopathia hyperostotica condensans* to the condition which he presumed to have arisen from mal-development of the limb bud, due to a metameric disturbance.

Meda (1927) recorded extensive involvement of a right upper limb with the condition. There was considerable deformity and limitation of movement of the affected hand, X-ray examination of which showed massive involvement of the middle finger and to a less extent of the adjacent halves of the index and ring fingers; the lower part of the humerus, the radius, and the middle carpal bones also were affected.

Valentin (1928) described details of a 17-year-old girl who since infancy had had slowly increasing limitation of movement of the right thumb and forefinger. The right upper limb was shortened and the index finger diverged from the middle finger, while movements of the forefinger, wrist, and elbow were restricted. On X-ray examination there was a patchy density of the bones of the affected limb extending from the shoulder joint to the terminal phalanx of the index finger.

Léri and Lièvre (1928) summarized existing knowledge concerning the seven cases which had been reported up to date. They described the condition as a hyperostosis involving all or practically all of the bones of one limb. In an upper extremity, the affected fingers are enormous, bossed, curved, divergent, and rigid. When a lower limb is affected, the appearance of the foot is less characteristic. There may be palpable thickenings of the long bones and the overlying skin may be thickened, red, shiny, and at times covered with varicosities. The hyperostosis, often very dense, extends in an irregular linear manner down one side of the affected bone, the appearance resembling the guttering of a candle or the running of metal. No bone need be affected in its entirety and it is characteristic of the disorder that it affects contiguous parts; the flat bones of the limb girdle may also be

involved. Often there is considerable limitation of movement of the limb from the mechanical effect of the bony deformities, but the joints themselves seem to escape direct involvement. The disorder develops during infancy or adolescence, is slow in onset, and sooner or later gives rise to the complaint of pain. Léri and Lièvre reported the result of the histological examination of a bony mass which had developed in the opposite infraspinatus muscle in Léri's original case during the six years in which it had been under observation. They found practically normal bone containing Haversian canals, many osteoblasts and a few osteoclasts, irregular islands of cartilage, and a richly cellular and vascular marrow with normal-looking vessels. As a result of the development of this bony mass and another one which had grown from the second rib on the same side as the affected limb, Léri and Lièvre put forward the view that the disorder was of parasitic origin and that embolic dissemination of infected osteoblasts had caused the development of the heterotopic bone.

Kauffmann (1928) reported the histological findings in Zimmer's (1927) case. He noted the compact formation of new bone, the presence of Haversian systems rather narrower than normal, and a fibrotic marrow containing occasional osteoblasts. He regarded the histological picture as inconclusive and felt that it gave no clue as to aetiology.

Meisels (1928, 1929) published details of a 25-year-old woman with involvement of the right lower limb. Her symptoms, which were of six years' duration, consisted of pain in the right knee and hip and a swelling of both legs. On examination there was a diffuse, heavy, non-pitting thickening of the lower part of the affected thigh, the skin of which was tense, shiny, and adherent to the underlying tissues, while there was a diffuse erythema associated with an abnormal distribution of vessels over the region of the hip; Meisels considered that these changes corresponded to Meigne's trophoedema. The limb was a little shortened, and radiologically changes characteristic of melorheostosis were present in the affected hip, femur, lower third of fibula, and part of the foot. As the basal metabolic rate was 36 per cent. above normal, Goldschlag (1929) attributed these changes to endocrine upset. He suggested that there was evidence of hyperthyroidism and hypopituitarism, and concluded that the bony changes were of constitutional and endocrine origin.

Kemkes (1930) described involvement of the right upper limb of a 54-year-old man. The limb had been weak, cold, and painful since the age of 17 years. The muscles of the thenar eminence were atrophied, while the thumb and forefinger were rigidly extended; movement of the elbow and wrist were limited and there was a palpable thickening of the ulna. Characteristic X-ray changes were present in the thumb and index finger, radius, part of the ulna, humerus, and scapula. Kemkes accepted Zimmer's theory regarding the aetiology of the condition.

Léri, Loiseleur, and Lièvre (1930) reported details of a 39-year-old man with involvement of the right upper limb. The right middle finger had been

stiff since infancy and latterly the patient had noticed pain in the corresponding hand and wrist. On examination there was a bony thickening of the proximal phalanx of the middle finger and of the third metacarpal bone on the back of the hand. The overlying skin was smooth, stiff, and adherent, but of normal thickness and colour; movements of the wrist and hand were restricted. Typical intermittent hyperostotic changes, extending from the scapula to the second and third fingers, were present in the affected limb. A biopsy was performed on the third metacarpal bone which was found to be bigger than normal, extremely hard, and of an ivory-white colour. Histologically, there was abnormality of outline and structure of the bony, lamellae and evidence of condensation and to a less extent of rarefaction. The condensation consisted of the deposit of an extremely dense bone, while the rarefaction was characterized by the disappearance of the normal lamellar pattern around the Haversian canals. No osteoblasts were seen and there was no evidence of any inflammatory reaction or the formation of new blood-vessels such as Putti had described. Bacteriological examination was negative and a subperiosteal graft of a fragment of affected bone on to the femur of a monkey was absorbed after eight weeks. The view was again expressed that the condition was of parasitic origin.

Junghagen (1930) described involvement of the right upper limb of a man who had had vague local pains since childhood. Weakness and limitation of movement of the affected limb had developed recently, and radiologically characteristic bony changes extended in an interrupted manner throughout the whole length of the limb. A specimen of bone removed from the olecranon process showed the histological features of eburnation. The lamellae were irregularly crowded together, the bone cells were narrow and less numerous than normal, the Haversian canals were also narrow, the blood-vessels infrequent, and in a few isolated areas their walls showed a small amount of lymphocytic infiltration. In considering the question of aetiology, Junghagen rejected Putti's (1927) theory that the bony changes were due to a vasomotor disturbance and accepted the explanation put forward by Zimmer (1927).

Kahlstorf (1930) described palpable tibial lesions in the left lower limb of a 33-year-old man, and concluded that the underlying pathological process arose primarily within the bone and slowly extended towards the surface; he also accepted Zimmer's (1927) explanation of its aetiology.

Piergrossi (1931) reported extensive changes in the right side of the pelvis and the right lower limb of a 36-year-old man. He recognized two phases in the development of the lesions—an initial osteosclerotic one characterized by slight enlargement and fairly regular outline of the affected bone, followed at a later stage by considerable irregular enlargement, presumably from periosteal proliferation. He accepted the ischaemic theory of Putti as the explanation of the bony changes.

Rokhlín (1931) described a much less extensive involvement of an upper limb in a 25-year-old woman, while Weil and Weismann-Netter (1932), reporting the disorder in the right upper limb of a 37-year-old man,

suggested the name of rheostosis in view of the involvement of the chest wall at the site of attachment of the affected limb.

Kraft (1932, 1933) reviewed existing knowledge concerning the disorder and reported two further cases. He described the lesions as consisting of a dense hyperostosis, resembling sclerotic bone, which extended in the form of longitudinal bands down the affected limb. He expressed the view that the strips of density within the cortex represented hyperostotic ridges on the surface of the bone, and that the unaffected adjacent bone frequently showed decalcification and rarefaction. Other features to which he drew attention were the occasional presence of bony masses in the soft tissues of the affected limb girdle, the varying fixation of the joints which occurs as the result of deposits in the periarticular areas, and the absence of pathological fracture. He proposed a useful classification based on the varying extent of the lesions, believing that the suggested grouping merely represented different stages in the process of the disease—complete continuous flow (most advanced stage), partial continuous and interrupted flow (advanced stages), circumscribed flow (early stage). In his first case, that of a 40-year-old man, a hard nodule had been present in the radial side of the left wrist for 19 years. A small lump had developed subsequently over the left clavicle, while the radial part of the left index finger had been noticed to be thick and uneven for 10 years. The corresponding humerus had also enlarged, and for four years nodules had been present on the left thumb and the deformity of the affected fingers had increased. The most noticeable physical signs were the presence of a large bony mass in the subclavicular region and several smaller ones in the pectoral area of the affected limb, an irregular thickening of the humerus and radius, and a nodular deformity of thumb and index finger. The radiological appearance of these widespread lesions was characteristic of melorheostosis. Whilst the patient was under observation, the limb became congested and oedematous and the skin developed small erythematous areas and became indurated. Kraft's second case, that of a 30-year-old woman, had been reported one year earlier by Geschiekter (1931) as suffering from ossifying periostitis. For seven years there had been increasing pain and limitation of movement of the right hip, resulting finally in complete immobility of the joint. On X-ray examination, there were changes typical of melorheostosis in the hip and the proximal three-quarters of the femur.

Saupe (1932) reported involvement of an upper limb in a 26-year-old woman who had had increasing swelling and deformity of the second and third fingers of the left hand since girlhood. On examination, there was a marked nodular bony deformity of these fingers which, like the affected elbow, were restricted in movement. Bony changes extending throughout the whole length of the limb were found on X-ray examination.

Woytek (1933) reported details of a 29-year-old man with lesions suggestive of melorheostosis arising from the lumbar spine. The patient had had a long-standing deformity of the lumbar region and had complained

of an aching pain in the back and upper limbs for several years. Radiologically, dense masses of bone could be seen extending from one side of the lumbar spine into the adjacent soft tissues; the base of the skull and both petrous bones were also extremely dense and there was distinct hyperostosis of the upper two ribs on the right side. Material for biopsy was obtained from the deformity in the lumbar region. The bone was very hard and dense with narrow Haversian systems, surrounded by even lamellae running in various directions; the bony trabeculae were coarse and uneven, the marrow spaces were small, and here and there osteoblasts were to be seen.

Moore and De Lorimier (1933) reviewed the literature and gave details of involvement of the left lower limb of a 38-year-old man. The patient had noticed dull aching pains in the feet and calves associated with oedema of the ankles for 16 years. As time passed, he developed sharp lancinating pains in the left thigh and weakness of the whole of that limb. There was limitation of movement of the thigh and knee, muscular atrophy along the posterior and lateral aspects of the thigh and leg, and palpable bony irregularities in the upper femoral region. X-ray examination revealed typical bony changes extending from the great trochanter to the calcaneus. The authors suggested that subperiosteal telangiectases of congenital or developmental origin might be the underlying cause of the lesions in melorheostosis. They thought that subperiosteal haemorrhages arising from such a condition of telangiectasis might cause cortical erosion and subsequent ossification and thus account for the various histological findings that had been reported in the condition.

Schor and Heinismann (1933) recorded the localized involvement of a thumb which had recently become thickened and deformed in a 20-year-old man; the X-ray changes, confined to the thumb and neighbouring carpal bones, were typical of melorheostosis.

Aldenhofen (1934) described the case of a 49-year-old man who had been subject to lumbago for 17 years. X-ray examination showed a marked localized density of the left half of the pelvis and, to a less extent, of the upper part of the corresponding thigh. The X-ray findings were unusual in that the normal contours of the affected bones were nowhere disturbed by the pathological process.

Hilton (1934) reported the unusual association of multiple rheostoses with familial chondrodystrophy. The patient, a girl aged 10 years, had developed a recent painful swelling of the lower end of the left femur. On examination she was feverish (103° F.) and the lower end of each femur was enlarged, the left more so. Radiologically, there was a varying degree of hyperostosis of the femora, humeri, and left radius, while the vertebrae were small, irregular, and wedge-shaped, and the head of the left radius was dislocated forwards and outwards. The patient's mother and two maternal aunts were also similarly affected. Material for biopsy, taken from the lower end of the left femur, showed irregular bony trabeculae ramifying between which were short columns of very vascular and rather loose connective tissue; numerous

osteoblasts were present along the line of separation between the fibrous tissue and the bone. X-ray treatment was given to the femora, the bony tumours of which first increased and then markedly decreased in size. A reduction in the amount of new bone formation outside the periosteum and a decrease of pain in the legs with a rapid improvement in the general condition of the patient followed this treatment.

Michalowski (1935) recorded involvement of the right forearm and hand in a man aged 27 years. The fourth finger of the hand, which had been affected since boyhood, was thickened, deformed, and restricted in movement. The radiological changes were confined to the ulna, certain carpal bones, and the third and fourth fingers.

Widmann and Stecher (1935) reviewed the literature and described involvement of the left upper limb of a six-year-old boy. A peculiar deviation of the affected thumb had been noticed at birth. Unfortunately, an X-ray examination was not made until the boy came under observation six years later, when the whole length of the limb was involved in the hyperostotic process.

Storen (1936) described a girl aged 13 years in whom the right foot had been deformed since birth. On examination the right lower limb was shortened and there were characteristic bony changes extending from the femur to the third and fourth metatarsals; as often happens, only one bone of the leg, the fibula, was affected.

Dillehunt and Chuinard (1936) described a 10-year-old boy in whom the disorder was associated with evidence of widespread scleroderma. The left thigh had felt 'hard' since early infancy, and within a short time this hardness had spread down the leg and the overlying skin had become white and tough; it was also noticed that the child limped a little on account of slight shortening of the affected limb. On X-ray examination there were dense sclerotic areas of bone present in the left side of the ilium and the head of the corresponding femur, while in the upper part of the bone shaft the osteosclerosis was associated with areas of cyst formation. The entire length of the femoral shaft and the upper half of the tibia were affected by the streaking hyperostosis, and the medial tarsal bones became similarly involved whilst the child was under observation.

Gottlieb (1936) and Natvig (1936) both recorded typical instances of the disorder involving the right lower limb of patients aged six years and 40 years respectively.

Casuccio (1937) described an 11-year-old boy whose chief complaint was that he had walked with a slight limp for two years. On examination the right lower limb was a little lengthened and warmer than the unaffected one, while the right calf was thickened. X-ray examination showed that there was massive involvement of the right femur and tibia. Material for biopsy was obtained from the middle of the tibia. The periosteum was thick and hyperaemic and there was a layer of new bone on the surface of the cortex, which was thicker than normal and had the appearance of a sclerotic

sponge, while the medulla was dense, fibrotic, and contained numerous capillaries; Casuccio accepted Putti's explanation of the aetiology of the bony lesions.

Canigiani (1938) recorded details of a 30-year-old woman with a painful swelling of the right thumb. Radiologically, there was a sharply defined and strictly localized area of hyperostosis affecting the thumb and contiguous carpal bones.

Gillespie and Siegling (1938) described a seven-year-old girl in whom a deformity of the affected toes and a generalized induration of the skin and subcutaneous tissues of the right lower limb had been present since birth. The limb was a little shortened and was held partly flexed at the hip. An X-ray examination made at the age of one month was normal. At the age of seven years the appearance of scleroderma in the affected limb was severe and almost generalized, while the persistent abduction and slight shortening of the limb seemed to be due to the tightness of the subcutaneous tissues. An X-ray examination at this age revealed widespread hyperostotic changes extending from the pelvis into the affected foot. Gillespie and Siegling expressed the view that the absence of radiological change at the age of one month did not support Zimmer's theory concerning the nature of the disorder.

Okhotin (1938) described characteristic bony changes in the right lower limb of an 11-year-old girl. Bury (1939) recorded details of a 35-year-old woman with involvement of the left lower limb, and expressed the view that the affection of only one limb was not an essential feature of the condition. Hill (1939) reported extensive involvement of the left upper limb of a 20-year-old man in whom the bones of the affected fingers were irregularly enlarged. Boggan (1939) described a 30-year-old man in whom typical changes in the right lower limb were associated with the presence of local gummatous ulcers. Several firm and painless subcutaneous nodules could be felt in the outer part of the thigh and leg, while the lower end of the tibia and the bones of the foot were thickened.

Bertelsen (1940) recorded details of a woman aged 21 years with an irregular thickening of the right tibia of many years' duration. The radiological changes, which were confined to the middle third of the shaft of the bone in its medial half, consisted of several blurred and irregular transparent areas surrounded by what seemed to be distinctly sclerotic osseous tissue. The patient's mother also showed changes in the left radius suggestive of melorheostosis.

Franklin and Matheson (1942) have recently described unusual changes in a woman aged 41 years whose right lower limb since childhood had seemed a little longer than the left. A left-sided plantar fasciotomy had been done at that time in an attempt to correct a pes cavus which was due apparently to constantly walking on the toes of the left foot. Since then she had worn a high boot on the left foot, but no readjustment to the boot had been needed for 20 years. About 15 years before, some lumps had developed on the right side of the head and the right side of the lower jaw, and within a short time

similar changes had appeared in relation to the right ulna. These lumps had increased gradually in size, but for some years had remained unchanged. During recent years the patient had noticed that by the end of the day the right lower limb was so swollen that digital compression produced obvious local pitting. Her chief symptoms when examined were the excessive weight and inconvenience of the affected limb and occasional shooting pains in the right side of the head. There were no abnormal physical signs apart from the deformities due to the bony changes and the great increase in size of the right lower limb which was three inches longer than the left and considerably stouter. There were numerous varicose veins on the surface of this limb, while the overlying skin showed the usual changes associated with intermittent oedema. The radiological appearance of the affected bones was remarkable. There was massive formation of new bone on the inner aspect of the right femur along its whole length, while the bones of the leg and foot were also involved to a less extent. The lumbar and cervical vertebrae (right side) were affected slightly, while in the right upper limb there was considerable hyperostosis of the ulna and the bones of the inner fingers. The appearance of the skull was extraordinary in that there was massive formation of new bone in relation to the right half of the mandible and the right side of the cranium in an area approximating to the cortical distribution of the middle cerebral artery, while the corresponding sphenoidal and nasopalatine regions were also involved in the process.

Case Report

Full clinical details will be found elsewhere (Hall, 1940); the present account is limited to a description of the bony lesions.

History. The patient, a boy aged 17 years, had been under personal observation for 4½ years on account of fits and symptoms of raised intracranial pressure due to tubercle sclerosis. When he was three years old, his right thumb and forefinger were noticed to be deformed. The deformity increased as the years passed, and movement of the affected fingers became increasingly restricted. He had had several injuries. At the age of three years he had fallen out of his perambulator and had fractured the right forearm, while in his seventh year he had fallen down a ladder from a height of 20 feet and had fractured the pelvis and once again the right forearm. He had not had any other symptoms referable to the limbs apart from an occasional aching pain along the whole length of the left lower limb during the last three years of his life.

Examination. He was a slightly undersized boy of subnormal mentality with typical facial adenoma sebaceum and well-marked evidence of raised intracranial pressure. The radial half of the right hand was very deformed (Plate 11, Fig. 1). The proximal part of the thumb was enlarged to form a hard nodular swelling on its ventral aspect, while the forefinger, the skin of which was tense, shiny, and adherent to the underlying tissues, was considerably enlarged and very nodular; there was severe limitation of movement of both these fingers. The proximal part of the middle finger was a little expanded, while the distal two-thirds were displaced mesially by the

TABLE I. *Summary of Published Cases*

Case	Author	Year	Sex	Age of patient	Age at onset	Site of lesion	Involvement of skin (S.) and subcutaneous tissue (S.T.)	Associated condition	Biopsy	Post mortem
1	Léri and Jeanny	1922	F.	30	10	L.U.L.	S.	—	+	—
2	Levin and MacLeod	1925	M.	35	6	R.U.L.	S.	—	—	—
3	Muzi	1926	F.	10	5	L.L.L.	—	—	—	—
4	Putti	1927	F.	8	Infancy	L.L.L.	—	—	+	—
5	Zimmer	1927	M.	32	21	L.L.L.	S.	—	+	—
6	Meda	1927	Not stated	Not stated	Not stated	R.U.L.	—	—	—	—
7	Valentin	1928	F.	17	2	R.U.L.	S. + S.T.	—	—	—
8	Meisels	1929	F.	25	21	R.L.L.	—	'Trophoedema'	—	—
9	Kemkes	1929	M.	54	17	R.U.L.	—	—	—	—
10	Léri, Loiseleur, and Lièvre	1930	M.	30	Infancy	R.U.L.	S.	—	+	—
11	Jungbagen	1930	M.	Adult	Childhood	R.U.L.	—	—	+	—
12	Kallstorf	1930	M.	33	30	L.L.L.	—	—	—	—
13	Milani	1930	M.	Not known	Not known	R.L.L.	—	—	—	—
14	Piergrossi	1931	M.	36	14	R.L.L.	—	—	—	—
15	Rokhlin	1931	F.	25	14	L.U.L.	—	—	—	—
16	Weil and Weismann-Netter	1932	M.	37	22	R.U.L.	—	—	—	—
17	Kraft	1932	M.	40	21	L.U.L.	S.	—	—	—
18	Kraft	1932	F.	30	23	R.L.L.	—	—	—	—
19	Saupo	1932	F.	26	Girlhood	L.U.L.	—	—	—	—
20	Woytek	1932	F.	29	Adolescence	L.S.	—	—	—	—
21	Moore and De Loriniier	1933	M.	38	22	L.L.L.	—	—	+	—
22	Schor and Heinismann	1933	M.	20	19	L.L.L.	—	—	—	—
23	Aldenhofen	1934	M.	49	32	U.L.	—	—	—	—
24	Hilton	1934	F.	10	10	L.L.L.	—	—	—	—
25	Michalowski	1935	M.	27	11	R. and L.L.L.	—	Chondrodystrophy	+	—
26	Widmann and Stecher	1935	M.	6	Birth	R.U.L.	—	—	—	—
27	Støren	1936	F.	13	Birth	R.L.L.	—	—	—	—
28	Dillehant and Chuinard	1936	M.	10	Infancy	L.L.L.	—	—	—	—
29	Gottlieb	1936	M.	6	Infancy	R.L.L.	S. + S.T.	'Scleroderma'	—	—
30	Natvig	1936	M.	40	30	R.L.L.	—	—	—	—
31	Casuccio	1937	M.	11	9	R.L.L.	—	—	—	—
32	Canigiani	1938	F.	30	Recent onset	R.U.L.	—	—	+	—
33	Gillespie and Siegling	1938	F.	7	Birth	R.L.L.	S. + S.T.	'Scleroderma'	—	—
34	Okhotin	1938	F.	11	Recent onset	R.L.L.	—	—	—	—
35	Bury	1939	F.	35	Recent onset	L.L.L.	—	—	—	—
36	Hill	1939	M.	20	9	L.U.L.	—	—	—	—
37	Boggon	1939	M.	30	28	R.L.L.	—	—	—	—
38	Bertelsen	1940	F.	21	Childhood	R.L.L.	—	Syphilis	—	—
39	Hall	1940	M.	16	3	R.U.L.	S.	Tuberoso sclerosis	—	—
40	Franklin and Matheson	1941	F.	41	Childhood	Widespread in right side of body	—	—	—	+

(This table may be incomplete as, owing to existing war conditions, there are a few publications concerning the disorder which are at present unobtainable in this country.)

increased width of the forefinger; the inner two fingers, particularly the ring finger, were unusually thin and tapering. At the base of the thenar eminence, the subcutaneous tissues were slightly thickened to form part of an apparently fluctuating and painless swelling which seemed to involve the sheaths of the flexor tendons. The only other skeletal abnormalities were the loss of the terminal phalanx of the left ring finger as the result of an accident and the presence of a hydrocephalic skull. The serum-calcium was 10.3 mg. per 100 c.c., the plasma-phosphate 4.8 mg. per 100 c.c., and the serum-phosphatase 9.8 units (3.11.37). The blood Wassermann reaction was negative. X-ray examination (Plate 11, Fig. 2) showed that the bony changes were confined to the radial part of the right hand and largely to the ventral surfaces of the affected bones. The essential change was that of an extensive and irregular hyperostosis which was most marked in the bones of the forefinger and the first phalanx of the thumb. The second metacarpus, and to a much less extent, the metacarpus of the thumb, were also affected, but in contrast to the phalanges they were regular in outline. The more severely affected bones were considerably enlarged, and a 'shadow' outline of their ventral surfaces previous to the development of the lesion could be seen in thumb and forefinger. The only other bone affected was the first phalanx of the middle finger, which showed slight hyperostotic changes on the radial part of its ventral surface. None of the epiphyses or articular surfaces was affected, and the only other local abnormality observed was an absence of the sesamoid bone of the affected thumb. The radiological appearances of the lesions did not change with the passing of time. They remained confined to the radial half of the hand, and the epiphyses fused normally with the bone shafts. On one occasion (16.6.39) there seemed to be slight thickening of the right humerus, just above the elbow joint, but this was not confirmed subsequently. The radiogram of the skull showed the usual changes associated with prolonged and severely raised intracranial pressure.

Post-mortem report. Lesions characteristic of tuberosc sclerosis were found in the brain, the eyes, and the kidneys, and these structures are being made the subject of a separate investigation.

The following abnormalities were noted in the examination of the radial half of the affected hand. The skin over the ventral surface of thumb and forefinger was thick and tightly bound down by dense fibrous bands to the underlying tissues, which was particularly noticeable in the case of the index finger. On reflecting the skin, what seemed to be tiny whitish calcareous granules were seen in the soft tissues covering the bony deformities. The vascular and nervous supplies of thumb, forefinger, and middle finger were normal. At the base of the thenar eminence, apparently originating from the outer surface of the sheath of the long flexor tendon, there was a pale nodule of fatty tissue, the size of a small finger nail, infiltrating the deep surface of the flexor pollicis brevis. The only other abnormality noted at this stage of the dissection was the presence of a tiny nodule of tissue in the interior of the sheath of the flexor tendon immediately adjacent to the fatty structure just described. The first phalanx of the thumb (Plate 11, Figs. 3 to 5) was remarkable on account of a fusiform expansion of its ventral surface by the hard nodular swelling which formed such a prominent deformity during life. In the thumb and first two fingers, the flexor tendons occupied deep bony grooves on either side of which there was an irregular ridge of bone to which some of the previously mentioned dense fibrous bands were attached. A small amount of glairy gelatinous oedema covered these bony ridges. There was also slight grooving beneath the extensor tendon on the

dorsum of the second phalanx of the index finger. The bones of the forefinger (Plate 11, Figs. 3 to 5) were large and nodular. There was a rough excrescence on the radial side of the first phalangeal shaft and a much smaller one on the ulnar side of the metacarpo-phalangeal junction which was in direct contact with a similar opposing area on the radial side of the middle finger. The second metacarpus was much broadened, but had none of the irregularity or grooving of the phalangeal bones. The only bone of the middle finger which was affected was the proximal phalanx (Plate 12, Fig. 6) which showed slight radial irregularity and central grooving on its ventral surface. Section of the second metacarpus (Plate 12, Figs. 7 and 8) revealed a fairly uniform thickening of the bone shaft. In its ventral part there was an occasional tiny islet containing a thick homogeneous translucent substance which tended to exude through the cut surface of the bone. In transverse section, the first phalanx of the index finger (Plate 12, Fig. 9) consisted of a thickened shell of bone of which only that occupying the dorsal surface approximated to normal. The remainder of the bone was irregularly thickened, ill defined, and contained several tiny islets of a structureless viscid material on either side of the centrally placed groove of the flexor tendon. The most prominent feature in the longitudinal section of the proximal phalanx of the thumb (Plate 13, Fig. 10) was the even expansion of its ventral surface by a firm mass of homogeneous tissue which did not seem to be either cartilage or bone. There were also several tiny islets of this tissue, some resembling those found in the second metacarpus, present throughout the ventral part of the phalanx, the dorsum of which alone seemed to be normal. The first metacarpus (Plate 13, Fig. 11) showed some irregularity of outline on its ventral surface and was a little enlarged, while its dorsal surface seemed normal. Section of the first phalanx of the middle finger (Plate 12, Fig. 6) confirmed the view that the changes were confined to the radial half of the ventral surface of the bone. It was noticed that the medullary cavities of the affected bones were full of red marrow, while yellow marrow alone was present in the unaffected ones. A further point of distinction was the ease with which the affected bones could be cut; this was in marked contrast to the normal brittle resistance of the unaffected ones.

Microscopical examination. The following tissues from the hand were examined histologically—bone, skin of forefinger, fibrous tissue, median nerve, the fatty tumour from the wrist, and the nodule from the tendon sheath.

Median nerve. In the Marchi preparation there is evidence of considerable degeneration of the myelin sheaths; these changes (which are associated with some interstitial fibrosis and thickening of the perineurium) are not present in Weigert Pal preparations.

Fatty tumour. Its fatty nature is confirmed and there is no evidence of any other tissue being present.

Nodule from tendon sheath. This appears to be composed almost entirely of fibrous tissue and fat, and the nodule has the appearance of a small fibroma.

Fibrous tissue. Dense fibrous tissue alone is present, but the walls of the blood-vessels are unusually thick and fibrous.

Skin. This is much thickened and shows (Plate 14, Fig. 12) hyperkeratosis, a very thickened dense cutis, and diffuse fibrosis of the underlying tissues. The sweat glands are unaffected, and nowhere is there any lymphocytic infiltration, haemorrhage, or calcification. The blood-vessels are well formed and in places have unusually thick walls.

It seems certain that the degeneration of the median nerve is of recent onset. The boy died a lingering death and at autopsy, extensive changes of a toxic nature were found in the heart and kidneys. It is probable that the degeneration of the nerve is also of toxic origin and would have been found in other peripheral nerves had they been examined. It is concluded, therefore, that the condition of the nerve has no connexion with the bony lesions. The occurrence of heterotopic fatty tissue in tuberosclerotic has been stressed by Norman and Taylor (1940). It seems probable, therefore, that the occurrence of an intramuscular lipoma in the present case represents another instance of the failure of normal development of tissues which occurs in Bournville's disease; the small fibroma within the tendon sheath is probably also of similar origin. The changes in the skin and subcutaneous tissues (the latter probably representing an exaggeration of the normal fibrous tissue septa) are part of the pathology of the condition and will be considered in detail under the appropriate heading.

Bones. A modified nitric acid method was used to decalcify the bones and remove all fat. A further point of distinction between the affected and the normal bones was noticed here, for the former became decalcified half as quickly as the latter. Sections were stained with haematoxylin and eosin, haematoxylin and safranin, Mallory, van Gieson, fuchsin azur, and mucicarmine. In addition, grinding preparations were made by impregnating thin sections of the bones with fine emery powder.

Of those examined, the third metacarpus and its second phalanx alone were normal, and these constituted the only control bones obtained from the patient; additional controls were obtained from an anatomical specimen and from a hand which had been amputated on account of severe trauma. The pathological process consists of the profuse proliferation of membranous bone arising from the ventral part of the bone shafts of thumb (Plate 13, Figs. 10, 11), and forefinger (Plate 12, Figs. 7 and 9), and the radial half of the first phalanx of the middle finger (Plate 12, Fig. 6). As a result of this proliferative process, the affected bones show a varying degree of enlargement. This is most marked in the forefinger, which assumes giant-like proportions. This anatomical hypertrophy is associated with extreme vascularity of the bone and a degree of rarefaction amounting to histological atrophy. A 'shadow' outline, apparently representing all that remains of the ventral surface of the bone previous to the development of the lesion, can be seen in sections of the first phalanx of the thumb (Plate 13, Fig. 10) and the bones of the forefinger (Plate 12, Fig. 9). In some parts the bone is apparently normal, though where the lesion is most extensive, as in the second phalanx of the forefinger, there is little if any normal bone to be seen. In general, the transition from normal to affected bone is abrupt, though in places it is more gradual. Periosteum is present only in relation to the unaffected bone. Elsewhere its place is taken by a felt-work of connective tissue, into which ossification is spreading from the surface of the bone in an irregular manner. These spicules of developing bone are usually sharply defined from the surrounding unossified tissue, but here and there all distinction is lost and they merge imperceptibly. The structure of the periosteum covering the unaffected bone is normal, but over the abnormal bone its fibres cease and become lost in a felt-work of connective tissue (Plate 14, Fig. 13). This tissue is very avascular and relatively acellular. It consists (Plate 14, Fig. 14) largely of interlacing bundles of semitranslucent fibres the nuclei of which are noticeably more abundant near the spicules of

developing bone, round which there are numerous osteoblasts. Its fibres in relation to these spicules are very swollen and have the appearance of osteogenetic fibres which can be traced directly into the ossifying medium (Plate 14, Fig. 15). Islets of unossified tissue are present within the walls of the bones, the largest lying in the first phalanx of the thumb beneath the 'shadow' ventral surface immediately adjacent to the epiphyseal line (Plate 13, Fig. 10). Examination of serial sections shows that this apparently isolated mass of tissue is in reality continuous with, and has a similar structure to, the felt-work of connective tissue on the ventral surface of the bone, and is showing similar signs of commencing ossification. The abnormal bone is everywhere characterized by immaturity and by evidence of active osteogenesis in a connective tissue medium. Osteoblasts are numerous, particularly in the areas where ossification is proceeding, but osteoclasts are scanty (Plate 14, Fig. 16). The contrast between the normal and abnormal bone is striking. Whilst the normal shows the usual orderly, compact, and avascular structure, the abnormal (Plate 14, Fig. 17) is irregular in arrangement, excessively vascular, and much less dense; moreover it stains with much less intensity. Haversian systems in all stages of development are present. Some are fully formed, but for the most part they are represented by vascular loops running between slender bony trabeculae, the general appearance resembling cancellous rather than compact bone. A noticeable feature in all the sections is that in extent and degree ossification varies inversely with the vascularity. It apparently begins, and is certainly best developed, in those parts which are farthest from the blood-vessels, whilst in the areas of greatest vascularity the bony trabeculae are fragmentary in the extreme. The blood-vessels have well-formed walls and nowhere is there any evidence of malformation. While the terminal ones are composed solely of an endothelial lining surrounded by loose connective tissue, the larger vessels have unusually thick walls whose lumen in places is rather narrow. Finally, the growth of cartilage, everywhere undisturbed, is confined to the ends of the bones, and nowhere is there any evidence of inflammation, haemorrhage, or the formation of neoplastic tissue.

Chemical analysis. The calcium and phosphorus contents of bone and ash were determined in pieces of bone obtained from the first phalanx of the patient's forefinger (preserved in 10 per cent. formalin) and from a phalanx of an otherwise normal adult hand which had been amputated one day previously on account of trauma. The ash was prepared by extracting the bones with hot ethyl alcohol, removing all adherent tissue by gently rubbing with a cloth, drying to constant weight, and then incinerating.

TABLE II
Calcium and Phosphorus Contents of Ash and Bone

	Ash %	Ash		Ca/P in ash	Bone	
		Ca %	P %		Ca %	P %
Control	51.8	49.4	17.4	2.8	25.3	9.0
Patient	54.2	47.2	19.1	2.47	25.6	10.4

While it would be unwise to draw any definite conclusions from these results which were obtained from a single estimation, the tentative opinion may be expressed that there does not seem to be any obvious alteration in the calcium and phosphorus contents of the affected bones.

Discussion

It must be admitted, as Brailsford (1942) has emphasized, that in radiographic appearance the lesions which I have described differ from those of melorheostosis in that the abnormal bone is much less dense and massive in my case. Nevertheless, the many similarities which exist between them seem to me too close to justify the conclusion that there is any essential difference between them, and I regard my case as having a hyperostosis of the affected bones such as occurs in melorheostosis.

The post mortem was performed at a private house in circumstances which made it impossible to examine such structures as the parathyroid glands. Fortunately, however, there is every reason to believe that the disease is of local origin, and that its pathology is revealed by an examination of the affected bones and adjacent tissues. This examination reveals two outstanding features, the prolific intramembranous ossification of an immature type, and the local absence of periosteum. These findings suggest that the condition may represent a local disorder of osteogenesis, one of three processes in terms of which Harris (1926) suggested that all skeletal changes might be interpreted. It is proposed here to consider only those aspects of osteogenesis which have a direct bearing on the disorder under review and discussion will be limited to a study of the periosteum in relation to the formation and growth of bone.

Macewen's views on the periosteum. Macewen (1912) based his views concerning the periosteum on an experimental inquiry which he conducted into the growth of bone. In one of his experiments, most of which were performed on dogs during the growth period, he removed a strip of periosteum measuring one inch in breadth from the entire circumference of the shaft of the animal's right radius; the superficial tissues were also taken away so as to ensure the removal of any remnants of periosteum. In the centre of the denuded shaft a silver ring was made to encircle the bone so as to adhere closely to the shaft for two-thirds of its circumference while it extended beyond the bone for the remaining third. Examination of the specimen, made nearly 13 weeks later, yielded interesting results. In Macewen's own words,

'A layer of connective tissue continuous with the periosteum covered the previously denuded shaft of the bone. The silver ring was covered by new bone, and was completely hidden from view for over two-thirds of the circumference. At the part of the ring which had been made to bulge beyond the bone, the surface of the ring was still exposed, though the interval previously existing between the bone and the silver ring had been filled up by new osseous tissue which had also partly covered the thickness of the silver ring. The surface of the exposed silver ring was adherent to and closely invested by the connective tissue layer, which was continuous with the periosteum above and below, and yet there was no bone formed between the outside of the ring and the newly-formed connective tissue which adhered to it.'

Commenting on the results obtained in this and other experiments, Macewen wrote:

'The osteoblasts emanating from the denuded bone covered the portion of the silver ring which was applied closely to two thirds of the circumference of the bone, and also filled the gap which existed between the bone and the bulged portion of the ring over the remaining third. Probably, had longer time been given, the osteoblasts emanating from the bone would have covered the remaining portion of the silver ring. It is to be noted that the connective tissue covering the bulged part of the ring, though closely applied to it, had not produced any ossific material to cover the silver ring. . . . When, in the canine species, the periosteum is entirely removed from the shaft of a long bone, and a silver ring is made to encircle the circumference of the denuded bone, the osteoblasts emanating from the exposed shaft are poured out peripherally, where they become ossified and increase the thickness of the bone, and at the same time cover the silver ring with fresh osseous tissue. Under suitable conditions the osteoblasts emanating from the bone penetrate the adjacent soft parts. This is seen in the ossific penetration of the newly-formed connective tissue and the exposed muscular bundles which thereby become infiltrated with ossified tissue and adherent to the shaft. . . . In one of the silver ring experiments, where a portion of the ring was not covered by osseous tissue, it was observed that the osteoblasts had been poured out from below and had flowed over the sides of the ring, where the mass had become consolidated as if it were lava in process of cooling.'

The outline in cross-section of the first phalanx of the forefinger in the present case is very similar to Macewen's diagrammatic representation of the above experiment (Text Fig., p. 100). Furthermore, his description of the newly formed bone corresponds closely to that found in melorheostosis—'a flowing hyperostosis resembling the guttering of a candle' (Léri and Joanny, 1922), 'the running of metal' (Léri and Lièvre, 1928). Macewen further pointed out that had the newly formed bone in his experiment arisen from the connective tissue covering the denuded shaft of the bone in place of the periosteum, it would have been distributed equally all over the ring. This consideration may be applied to melorheostosis, in which the hyperostosis originating from the shaft of the affected bone invades the adjacent tissues which undergo the changes associated with impending ossification.

Leriche and Policard's views on osteogenesis. Only certain aspects of the views of Leriche and Policard (1926) will be considered. These authors stress the similarity of the various forms of ossification whereby connective tissue is transformed into bone. They visualize three stages in the process, (1) the creation of an ossifiable medium whereby the connective tissue becomes oedematous and reverts to an embryonic state in which the fibrillary network multiplies and swells, (2) the infiltration of this medium with the preosseous substance which though not hard is viscous and resistant; both this and the previous stage seem to be the result of circulatory changes which at present are but little understood, (3) the deposition of calcareous material whereby

the procosseous substance is impregnated with lime salts and becomes hardened. They recognize two processes whereby resorption of bone occurs, osteoclasia and osteolysis, and believe that the latter is the more important and always results from an increase in the vascularity of the bone. They hold that further new bone may be formed through the liberation of calcium and the creation of a local calcific excess as a result of this resorption. It is this combination of anatomical hypertrophy with histological atrophy which is such a striking feature of melorheostosis in which the hyperostosis is associated with an excessively vascular rarefying process of the underlying bone. Intimately associated with this hypertrophic resorption of the affected bone is the local absence of periosteum. Leriche and Policard (1926) conclude, as did Maccwen and some of the earlier workers, that so far from having any osteogenetic role, the periosteum limits ossification. They note that fibrous tissue everywhere acts similarly and that membranous structures, fibrous and muscular tissues and aponeuroses, all have the property of limiting bone in process of formation. The flexor tendons in the present case likewise restrained the formation of bone in their immediate vicinity, while elsewhere the areas of periosteal deficiency were associated with the hyperostosis to which the disorder owes its name. Leriche and Policard hold that what has been called an irritated periosteum is merely a periosteum that has been modified by trauma or inflammation. Such a periosteum, congested, oedematous and thick, has the appearance of granulation tissue; in other words it has returned to the embryonic state and may be regarded as constituting an ossifiable medium. Occurring in the immediate vicinity of bone, these changes lead progressively to hyperaemia and resorption of bone, the creation of a local calcific excess, and the formation of further new bone. This concept may be applied to melorheostosis in which a local modification of the periosteum has occurred, not as a result of infection or trauma, but of some other factor the nature of which will be discussed when dealing with the question of pathogeny. The work of Leriche and Policard also explains the probable nature of the glairy oedema with which the hyperostosis is associated and the intraosseous islets of homogeneous material which have the histological appearance of connective tissue in process of ossification. The former presumably represents the oedematous infiltration which helps to create the ossifiable medium which Leriche and Policard state is a macroscopical rather than a histological phenomenon, while the latter clearly corresponds to the procosseous substance. The largest mass of this tissue was present within the shaft of the first phalanx of the thumb (Plate 14, Fig. 17) and, as already stated, was continuous with the connective tissue covering the hyperostosis. On the dorsal unaffected surface of the bone the periosteum was continuous with the perichondrium, while the bone of the diaphysis fused with that of the epiphysis. On the affected surface, however, where there was no periosteum, it was as if the process of membranous ossification, whereby the permanent shaft of a long bone is formed, had never quite reached the normally developing epiphyseal bone, with the result that

a layer of unossified tissue still separated epiphysis from diaphysis. It is presumably this absence of epiphyseal involvement which explains why the articular surfaces are never affected in melorheostosis.

Associated skin lesions. Repeated references are made in the literature to the state of the skin and subcutaneous tissues overlying the bony lesions—tight and slightly tender (Léri and Joanny, 1922), red, indurated, and tender (Lewin and MacLeod, 1925), tense and shiny (Zimmer, 1927), thick, red, and shiny, and at times covered with varicosities (Léri and Lièvre, 1928), evidence of trophoedema, consisting of a diffuse, heavy, non-pitting thickening of the thigh, the skin of which was tense, shiny, and adherent to the underlying tissue, while there was a diffuse erythema associated with an abnormal distribution of vessels over the region of the hip (Meisels, 1929), smooth, stiff, and adherent (Léri, Loiseleur, and Lièvre, 1930), erythematous and indurated (Kraft 1932, 1933), evidence of scleroderma, the affected thigh and leg feeling hard and the overlying skin becoming white and rough (Dillehunt and Chuinard, 1936), scleroderma, consisting of a generalized induration of the skin and subcutaneous tissues (Gillespie and Siegling, 1938), tense and shiny skin, adherent to the underlying tissues (Hall, 1940). The frequency of these changes suggests that they are an integral part of the disease. Of the nine cases in which they were present, they were sufficiently prominent in two (Dillehunt and Chuinard, 1936; Gillespie and Siegling, 1938) to be mistaken for scleroderma and once (Meisels, 1929) for trophoedema. The resemblance to Meigne's trophoedema (Milroy's disease) does not seem to be marked. There is, however, considerable resemblance to the appearance of the skin of scleroderma, though histologically there is no lymphocytic infiltration or atrophy of sweat glands such as occurs in that condition. It may be assumed, therefore, that all degrees of involvement of the skin and subcutaneous tissues occur in melorheostosis. Furthermore, in every case in which such changes have been present, the underlying bony lesions were severe, though this was sometimes so in the absence of any obvious involvement of the soft tissues. Presumably these changes tend to occur and be most marked in those cases in which the underlying bony lesions are severe and active from the early stages of development, but despite the severity of the skin lesions and the presence at birth of a deformity of the affected foot in Gillespie and Siegling's (1938) case, an X-ray examination made at the age of one month was normal. Further reference to this important point will be made when considering the nature and pathogeny of the disorder. It is perhaps significant that only the deeper layers of the skin, those of mesodermal origin which constitute the dermis proper, are affected. It is suggested that in the more severe forms of melorheostosis changes occur simultaneously in all the tissues which are affected, with the result that they form a suitable medium into which ossification may spread from the nearest local deposit of calcium, the adjacent bone. One tissue which is affected severely is the periosteum, in the local absence of which ossification 'overflows' from the bone into the adjacent tissues which, with the deeper layers

of the skin, react by becoming progressively fibrotic and so simulate the appearance of scleroderma.

Heterotopic bone. Leriche and Policard (1926) reject the views that heterotopic bone develops from the growth of an embryonic rest (Cohnheim), from periosteal displacement (Ollier), or from the dissemination of osteoblasts (Maeewen). They consider that the first step in its formation is the creation of an ossifiable medium by the reversion of pre-existing connective tissue to the embryonic state. They state that this occurs only as a result of inflammation or trauma, even in the absence of an organizing haematoma. Once this medium is formed, calcium is liberated from neighbouring bone and ossification results. Keith (1928), on the other hand, holds that the first step is the absorption of a foreign or dead body by the formation of a vascular bud in which there are cells which may become both osteoblastic and osteoclastic in their action. Whether bone will form depends on the presence of lime salts in solution and on some other factor or factors as yet unknown, one of which is almost certainly in the nature of an enzyme. It may be noted that both these views recognize the presence of a vascular factor. It is difficult to visualize the method of production of heterotopic bone in melorheostosis, in which as yet there is only one recorded instance of its occurrence (Léri and Lièvre, 1928), and for the present it may be regarded as uncertain whether it forms a feature of the pathology of the disorder.

Interpretation of pathological findings. Not only bone and periosteum, therefore, but also subcutaneous tissue and dermis may be affected in melorheostosis. The history that deformity of the affected part may be apparent at birth (Widmann and Stecher, 1935; Støren, 1936; Gillespie and Siegling, 1938) and the nature of the pathological process suggest that the disorder is of developmental origin. Attention has been directed already to the fact that radiological examination of Gillespie and Siegling's (1938) patient at the age of one month was negative, despite the presence at birth of a deformity of the affected foot and widespread changes in the skin and subcutaneous tissues. This absence of radiological change hardly seems to justify Widmann and Stecher's (1935) comment that Zimmer's (1927) theory concerning the aetiology of melorheostosis is invalidated. On the contrary, one can only assume that at such an early age, the pathological changes were not sufficiently advanced as to be apparent on X-ray examination. It is concluded, therefore, that melorheostosis is a local disorder of osteogenesis. The primitive nature of the bone, the condition of the periosteum, the not infrequent involvement of skin and subcutaneous tissue, and the occasional local 'atrophy' of muscle (Kemkes, 1930; Moore and De Lorimier, 1933) all suggest that for reasons at present unknown there has been some local inherent defect of the mesoderm. Bone, fibrous tissue, including periosteum and fascia, muscle, and dermis may all be involved and fail to attain full differentiation and development. This local tissue 'inferiority' is presumably also associated with defective powers of endurance and repair, the severity of which determines the onset of symptoms. If the defect be pro-

found, the condition is apparent at birth, while with lesser degrees of deficiency the onset of symptoms is delayed until infancy, childhood, or adult life. Without doubt the defect dates from the very early stages of development, no matter how late the onset of symptoms. Only so can involvement of the thumb at birth be explained, for that member is outlined in mesenchyme as early as the fourth week of development (Harris, 1934). It is noticeable that the bony changes always seem to have an axial distribution. Presumably the mesoderm of those embryonic somites which are concerned with the formation of the limb buds is especially liable to be affected. There does not seem to be any apparent reason why this should be so or why only two cases have been described so far in which more than one limb was affected (Hilton, 1934; Franklin and Matheson, 1942). The remarkable case recently described by Franklin and Matheson (1942) confirms the view that occasionally bone developed entirely 'in membrane' may also be involved, and proves that the condition may affect membrane and cartilage bone alike.

Association with tuberose sclerosis. This association may not be without significance. The nature of Bournville's disease is still in doubt, but there is increasing evidence to suggest that it is a developmental anomaly commencing early in foetal life (Critchley and Earl, 1932). In the fully developed condition the cerebral lesions may be associated with abnormalities in such varied structures as skin, retina, kidney, thyroid, thymus, heart, spleen, liver, bowel, and breast. These structures have one feature in common—they all contain, and some are derived solely from, tissue of mesodermal origin. It is possible that these widespread lesions may be the expression of a metaplasia primarily affecting mesodermal tissue to a greater extent than is generally conceded. If this be so, the association of melorheostosis with tuberose sclerosis may be explained on the basis of a mesodermal defect of unusual distribution and type.

Summary and Conclusions

1. The literature concerning melorheostosis is reviewed.
2. An account is given of the post-mortem investigation of the bony lesions of a case in which death occurred from the effects of raised intracranial pressure due to tuberose sclerosis.
3. The pathological findings are discussed with reference to the development and growth of bone.
4. It is concluded
 - (a) that despite certain radiographic differences the lesions in question correspond to the changes which occur in melorheostosis.
 - (b) that this disease may affect any part of the skeleton where membrane bone is formed, though essentially it is a disturbance of ossification in connexion with diaphyseal bone (that is, that originally laid down in cartilage).

(c) that it may be defined as a local disorder of osteogenesis, characterized by periosteal deficiency and a spread of ossification from the affected bone into adjacent tissues.

(d) that it is due to some inherent tissue defect such as is believed to constitute an abiotrophy in the sense described by Gowers (1902), whereby the affected tissues not only fail to attain full normal development and differentiation, but are also defective in their powers of vital endurance.

(e) that the tissues affected, bone and periosteum, fibrous and connective tissue, muscle, and dermis, are of mesodermal origin, and that their varying involvement determines the age of onset of symptoms.

(f) that as a result of the periosteal deficiency there is an extension of the process of ossification from the affected bone into adjacent tissues.

(g) that the ossification is intramembranous and immature in type.

(h) that involvement of the skin and subcutaneous tissue is part of the pathology of the disorder.

(i) that this study supports the view that physiologically periosteum limits the growth of bone.

5. It is suggested that the association of melorheostosis and tuberosc sclerosis may be the expression of a mesodermal defect of unusual distribution and type.

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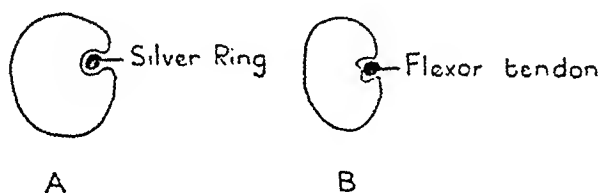
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- a. Schematic representation of Macewen's experiment.
b. Outline of cross-section of first phalanx of author's case.



FIG. 1. Photograph of patient to show: 1. Deformity of affected fingers. 2. Facial adenoma sebaceum. 3. Macrocephaly due to severe internal hydrocephalus



FIG. 2. Radiograph of affected hand, 4.4.40



FIGS. 3-5. Photographs of affected fingers after removal of soft tissues to show: 1. Nodular enlargement of base. 2. Central grooves occupied during life by flexor tendons



FIG. 6. Transverse section first phalanx of middle finger ($\times 4$), showing lesion confined to radial half of bone



FIG. 7. Transverse section second metacarpus ($\times 4$); the more normal darkly staining bone is largely confined to the inner dorsal aspect of the section

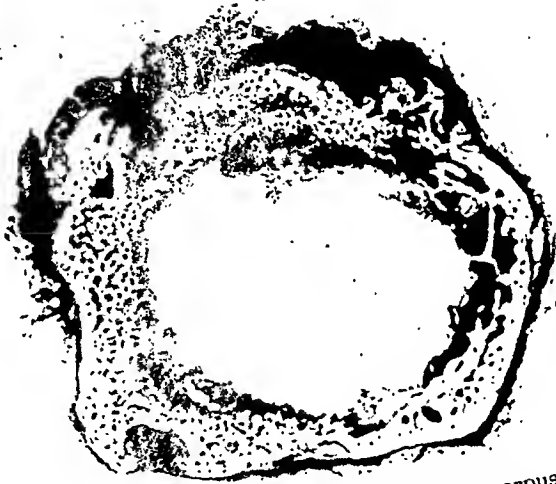


FIG. 8. Grinding preparation second metacarpus ($\times 4$); only the inner aspect of the bone is normal



FIG. 9. Transverse section first phalanx of forefinger ($\times 4$). The more normal darkly staining bone is confined to the dorsal surface; numerous areas of unossified tissue are present in the affected bone, the rarefied

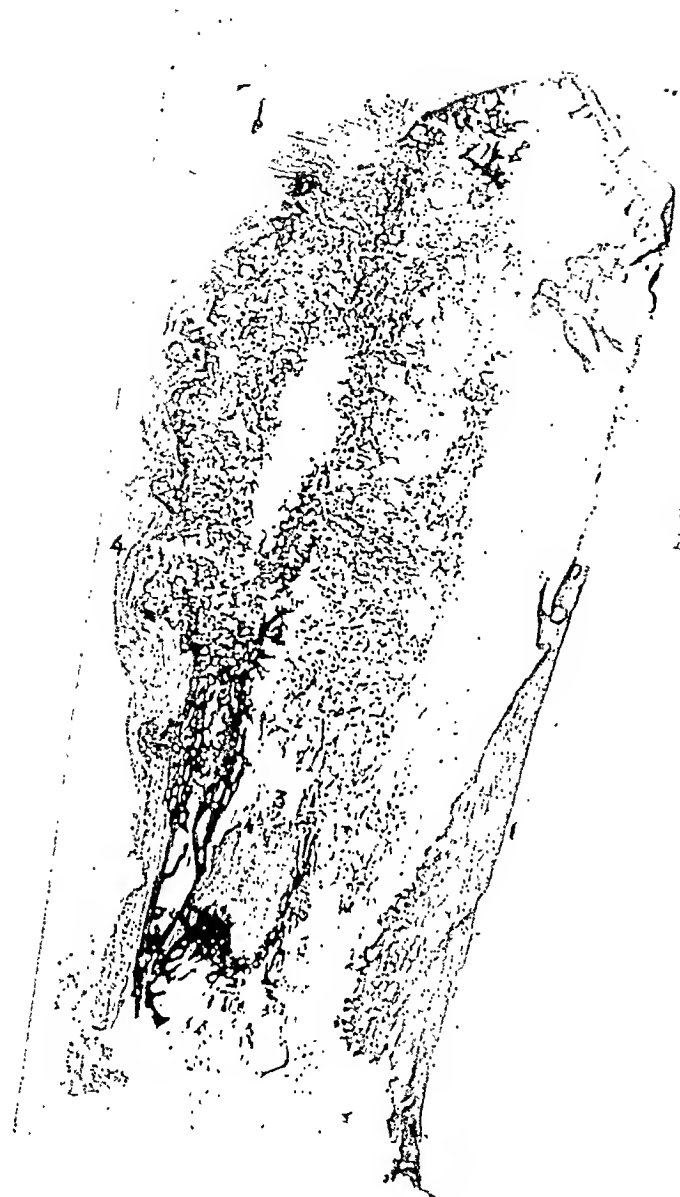


FIG. 10. Longitudinal section first phalanx of thumb ($\times 4$)

- Note 1. The more normal and darkly staining dorsal surface of the bone covered by periosteum
2. The 'shadow' ventral surface at the base of the hyperostosis
3. The mass of unossified tissue within the bone shaft in a para-epiphyseal position
4. The connective tissue on the ventral surface of the bone into which ossification is extending in an irregular manner



FIG. 11. Transverse section, first metacarpus ($\times 4$), showing lesion confined to ventral surface of bone

main groups on the basis of their shapes, into 'tailed' curves, 'diagonal' curves, and 'normal type' curves (Fig. 1). Only one of the 24 curves studied before splenectomy was intermediate in type and difficult to classify.

In the 12 cases with 'tailed' curves haemolysis could first be detected with saline of concentration between 0.76 per cent. and 0.58 per cent. and only gradually increased in amount with diminishing saline concentration until a point was reached at which 10 to 20 per cent. of the erythrocytes

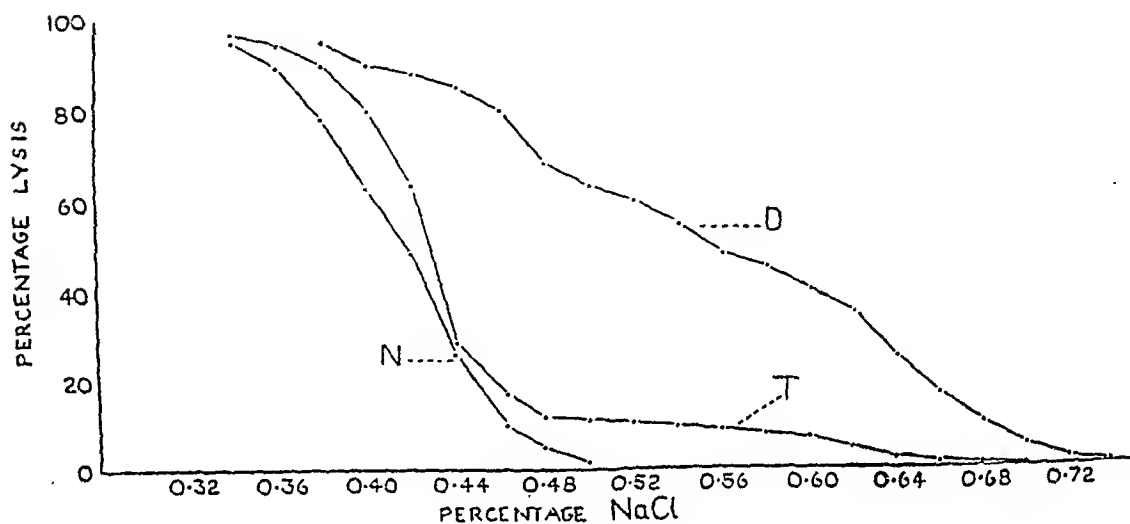


FIG. 1. Quantitative fragility curves from three patients with familial haemolytic anaemia. D = 'diagonal' curve, T = 'tailed' curve, N = 'normal' curve.

were broken up. Beyond this critical point the curve became abruptly steeper and of approximately the same slope as in the normal person.

'Diagonal' curves were found in six cases; in these haemolysis was first perceptible with saline between 0.80 per cent. and 0.68 per cent. and increased fairly steadily as the concentration was reduced. In four of the cases there were one or more flattened zones towards the middle of the curve.

In the five cases with 'normal type' curves the increase in fragility was only slight; lysis was first apparent in saline between 0.54 per cent. and 0.46 per cent. and the curves were of normal shape, falling within the normal limits of slope described by Vaughan (1937). Her method of calculation, which presupposes a symmetrical curve, is not applicable to 'tailed' curves.

Vaughan (1937) stated that acute haemolytic crises and severe anaemia were usually associated with flatness of curve. In the present series, the haemoglobin percentage estimated by Haldane's method in the five cases with 'normal type' curves varied from 56 to 97 per cent., with a mean of 76 per cent.; in the 12 cases with 'tailed' curves it varied from 51 to 91 per cent. with a mean of 68 per cent., while in the six cases with 'diagonal' (that is, flatter) curves the percentage lay between 22 and 74, with a mean

of 49. These results are in general agreement with Vaughan's statement, but the series is too small for the differences to be statistically significant.

A quantitative technique for fragility estimation has not been commonly employed, and few curves made from patients with familial haemolytic anaemia have been published since those figured by Chauffard (1907). Two

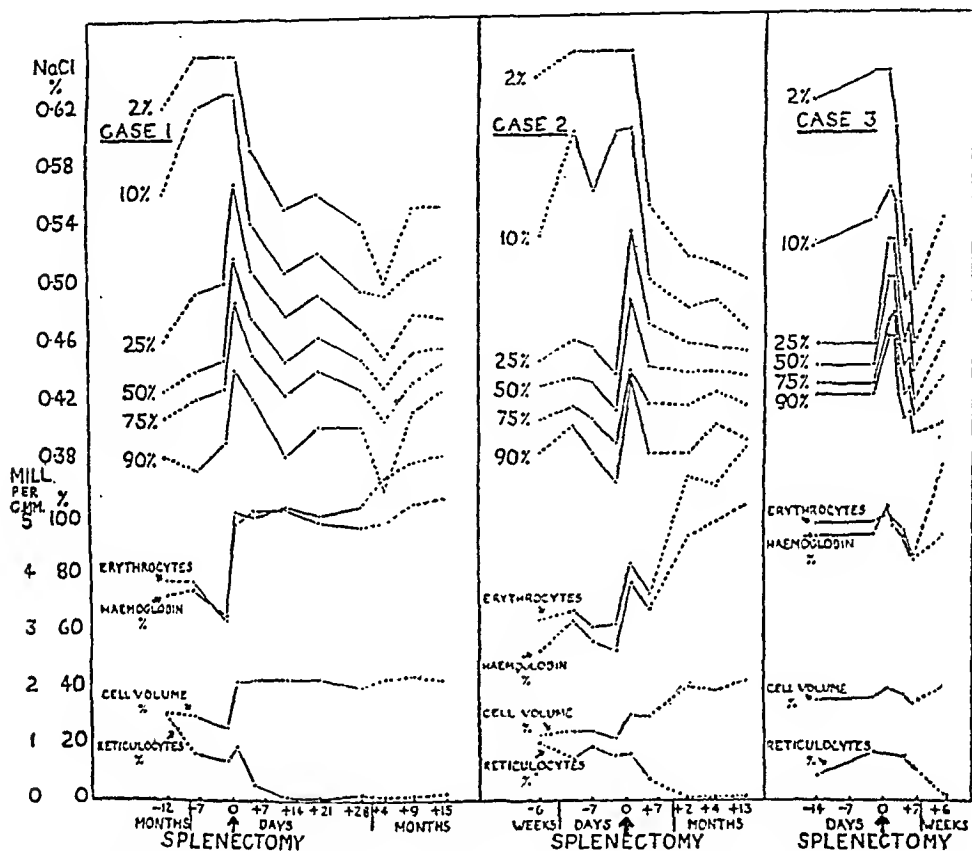


FIG. 2. Changes in fragility, erythrocyte count, haemoglobin, cell volume, and reticulocyte percentages produced by splenectomy (Cases 1 to 3). Interrupted lines link isolated observations; continuous lines indicate observations made at relatively close intervals. Fragility is expressed by recording the saline concentrations in which there was 2, 10, 25, 50, 75, and 90 per cent. haemolysis.

curves are shown in Dawson's (1931) paper; Whitby and Hynes (1935). Dacie and Vaughan (1938), Cassells (1938), Waugh and Lamontagne (1940) each show a single curve, and two curves, one from a mild and the other from a severe case, are shown in Vaughan's (1937) paper. Whitby and Britton (1939) stress the importance of a quantitative technique and say that much of the fragility curve may be within normal limits with only traces of haemolysis in the higher concentrations of saline which appear as a 'tail' at the right-hand end of the curve, outside normal limits.

The effect of splenectomy on the fragility curve (12 cases). In nine patients repeated observations were made before and after splenectomy. Seven of these had 'tailed' curves; they all showed 24 hours after operation a transient

increase in median fragility (that is, the concentration of saline giving 50 per cent. haemolysis). There was no appreciable alteration in the point of initial lysis at this time, but the shifting to the right of the steep middle part of the curve indicated an increased proportion of the fragile cells previously present only in small numbers and responsible for the tail of the

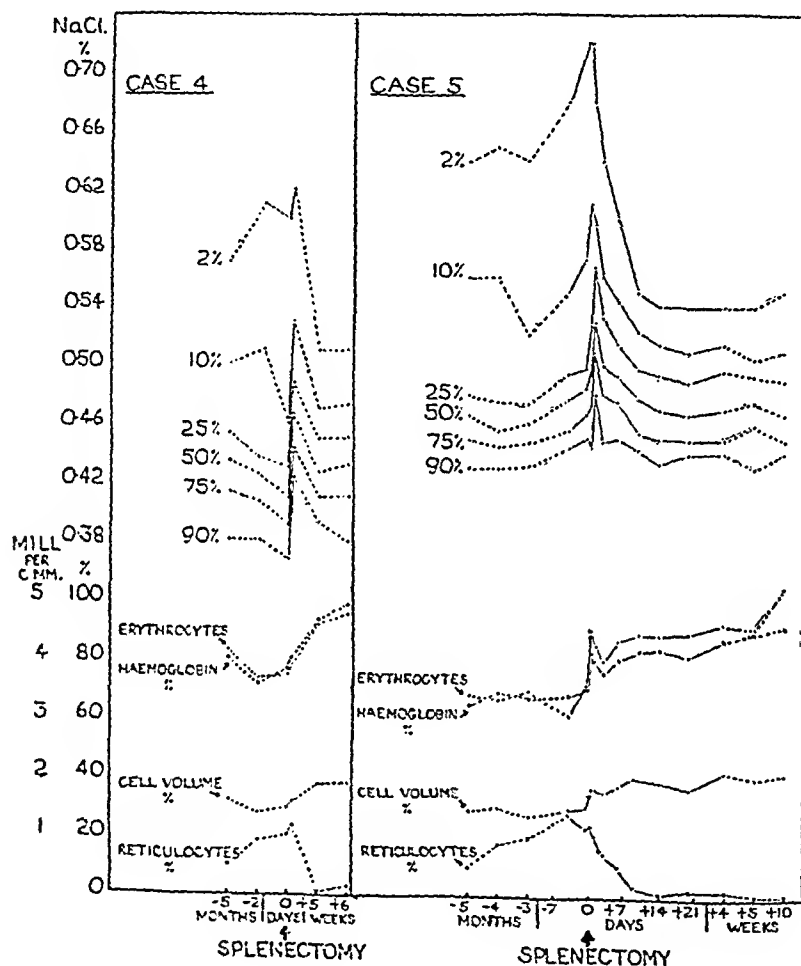


FIG. 3. Changes in fragility, erythrocyte count, haemoglobin, cell volume, and reticulocyte percentages produced by splenectomy (Cases 4 and 5). Interrupted lines link isolated observations; continuous lines indicate observations made at relatively close intervals. Fragility is expressed by recording the saline concentrations in which there was 2, 10, 25, 50, 75, and 90 per cent. haemolysis.

curve (Figs. 2 to 5). By the third day after splenectomy a reduction in fragility was evident, and during the latter half of the first week the median fragility of all the cases fell towards the pre-operative level, the tails of the curves having by then largely disappeared. By the tenth day the shape of the curves was nearly normal and median fragility at or slightly below the pre-operative level. Cases 1 and 2 were followed 15 and 13 months respectively after splenectomy; the fragility showed only minor fluctuations and

remained well outside normal limits (Fig. 2). Three patients (Cases 5, 6, and 7) were studied more completely on the day of splenectomy; fragility was estimated before anaesthetization, after the induction of anaesthesia but before the start of the operation, and at the end of the operation. In each case an increase in fragility was produced by anaesthetization, and

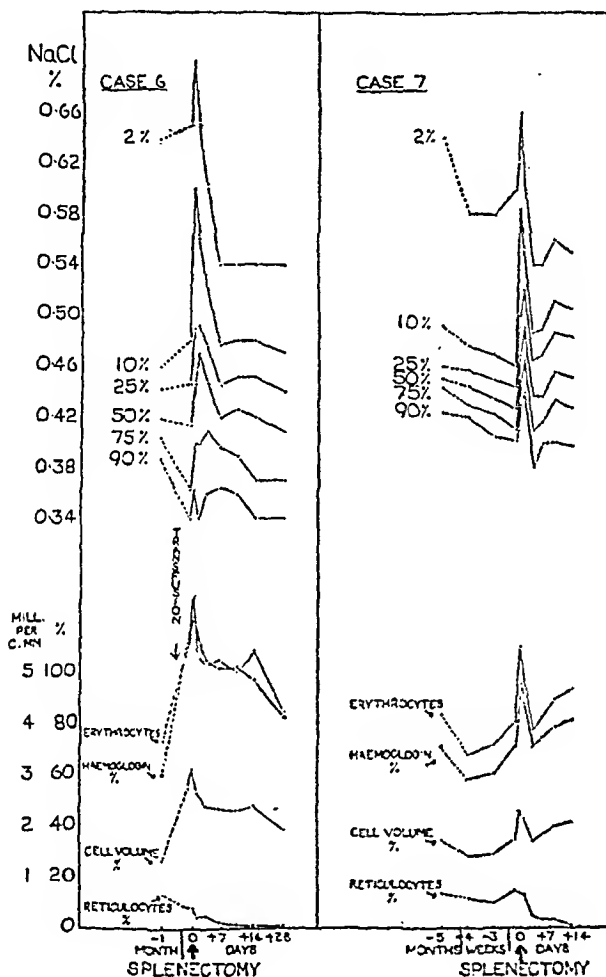


FIG. 4. Changes in fragility, erythrocyte count, haemoglobin, cell volume, and reticulocyte percentages produced by splenectomy (Cases 6 and 7). Interrupted lines link isolated observations; continuous lines indicate observations made at relatively close intervals. Fragility is expressed by recording the saline concentrations in which there was 2, 10, 25, 50, 75, and 90 per cent. haemolysis.

a further substantial increase had occurred by the time the operation had been concluded (Fig. 6).

Case 8 proved interesting. The patient was a woman, aged 47 years, who had previously enjoyed good health, but complained of intermittent jaundice of at least 10 months' duration. The family history was negative, but this was not verified. When her blood was first examined it was found to contain 56 per cent. haemoglobin, and 2,400,000 erythrocytes per c.mm., with

25 per cent. reticulocytes, and numerous spherocytes could be seen in stained films. Splenectomy was performed and the spleen found to weigh 560 gm.; histologically, it was seen to be identical with Cases 1 to 7. Her blood was examined 12 times during the first three weeks after splenectomy. The fragility curve before operation was of the 'normal type' for familial haemolytic

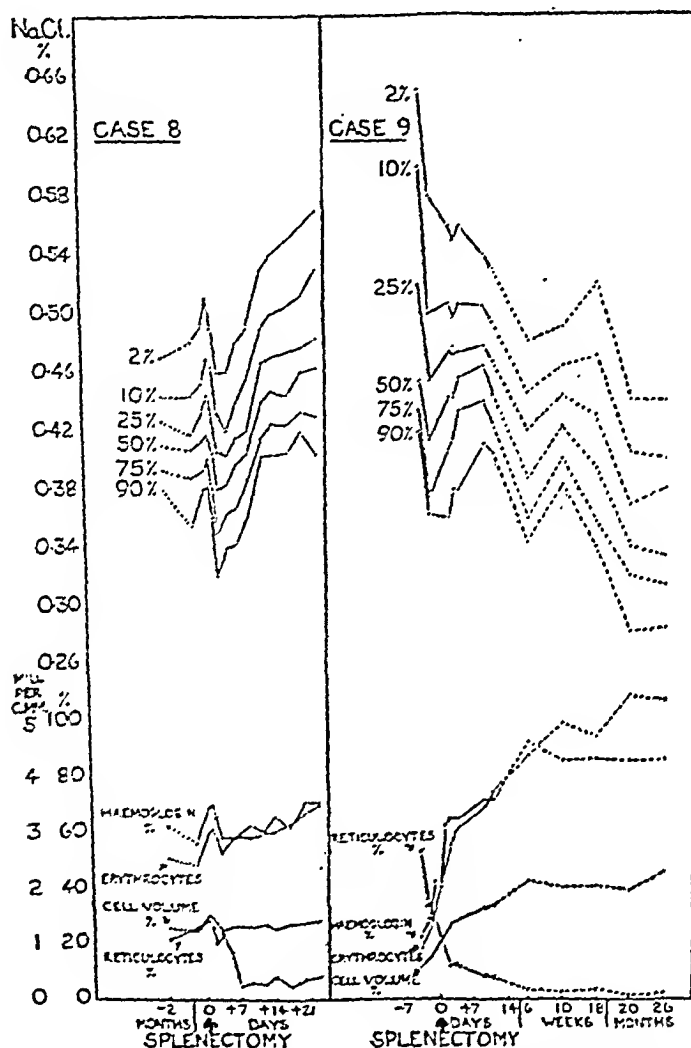


FIG. 5. Changes in fragility, erythrocyte count, haemoglobin, cell volume, and reticulocyte percentages produced by splenectomy (Cases 8 and 9). Interrupted lines link isolated observations; continuous lines indicate observations made at relatively close intervals. Fragility is expressed by recording the saline concentrations in which there was 2, 10, 25, 50, 75, and 90 per cent. haemolysis.

anaemia, but slightly less steep, and well outside normal limits. A small transient increase in fragility 24 hours after splenectomy was followed by a fall to normal by the third day except for a small 'tail' representing 2 per cent. of cells. This was succeeded by an almost steady increase in fragility to well above the pre-operative level (Fig. 5). During the three weeks after splenectomy progress was slow and disappointing, with a rise in

erythrocyte count from 3,060,000 to 3,520,000 per c.mm. only. Her reticulocytes, however, had dropped from 26 per cent. to 5 per cent. by the seventh day, but fluctuated between 5 and 8 per cent. during the next fortnight. She then left hospital and was not seen again until three years had elapsed, when she was found to have made an excellent recovery. Examination of her blood gave the following results—erythrocytes 4,210,000 per c.mm. with 3.7 per cent. reticulocytes, and haemoglobin 91 per cent. Fragility was increased, but the cells were a little less fragile than when she was last examined, although more fragile than before splenectomy.

Case 9 was also a diagnostic problem. A girl of 21 years was admitted to hospital in a severe haemolytic crisis of three weeks' duration; her previous health had been good except for bilious attacks during adolescence, and the family history was negative. On admission her blood count showed 900,000 erythrocytes per c.mm., with 55 per cent. reticulocytes, and the haemoglobin was 22 per cent. Fragility was greatly increased and the curve was of the 'diagonal' type; 2,500 c.c. of citrated blood slowly transfused over a period of 47 hours raised the haemoglobin only to 40 per cent. Splenectomy was then performed and during the operation she received a further 1,000 c.c. of citrated blood. The following day she was obviously better and the haemoglobin was 62 per cent., and slowly rose to 72 per cent. during the next 10 days, with an increase in erythrocytes from 2,740,000 to 3,680,000 per c.mm., and a fall in reticulocytes to 8 per cent. Ten weeks later erythrocytes were 4,950,000 per c.mm., haemoglobin 85 per cent., and reticulocytes 2 per cent. The fragility changes were interesting (Fig. 5); a post-operative increase was found rising to a maximum about the ninth day after splenectomy, associated with a progressive loss of the tail of the curve. No estimation of fragility was made on the day after operation, so a more transient post-operative rise may have been missed. Twenty months after splenectomy her cells were more resistant than normal, and this finding was confirmed six months later. Her spleen weighed 650 gm.; the pulp was congested and there was slight hyperplasia of the reticulum cells. This case and the one previously described (Case 8) are difficult to classify with certainty, and although the family history was negative in both, when first seen there appeared to be no valid reason for not considering them true examples of familial haemolytic anaemia, and they are for this reason included in the present series. The ultimate disappearance of abnormal fragility in Case 9 suggests that the correct diagnosis in this case should have been 'acute haemolytic anaemia, of unknown origin'. It is likely that a study of the survival time of normal blood after transfusion into atypical cases, such as these, would aid in their differentiation. Dacie and Mollison (1943) transfused a series of patients suffering from haemolytic anaemia of varied type, but only in typical familial haemolytic anaemia and in chronic haemolytic anaemia with nocturnal haemoglobinuria was survival found to be normal.

Three other patients were examined before splenectomy and during convalescence; two of them had greatly increased fragility, and the curves

were of the 'diagonal' type with zones of flattening. In one patient the concentration at which 2 per cent. lysis occurred was reduced from 0.78 per cent. to 0.60 per cent. saline 18 days after operation, but the curve remained less steep than normal. The second patient similarly showed a reduction in the point of 2 per cent. lysis from 0.70 per cent. to 0.64 per cent. saline 17 days after splenectomy. The third patient had a curve of the 'tailed' type; 14 days after splenectomy the 'tail' had been largely lost, with

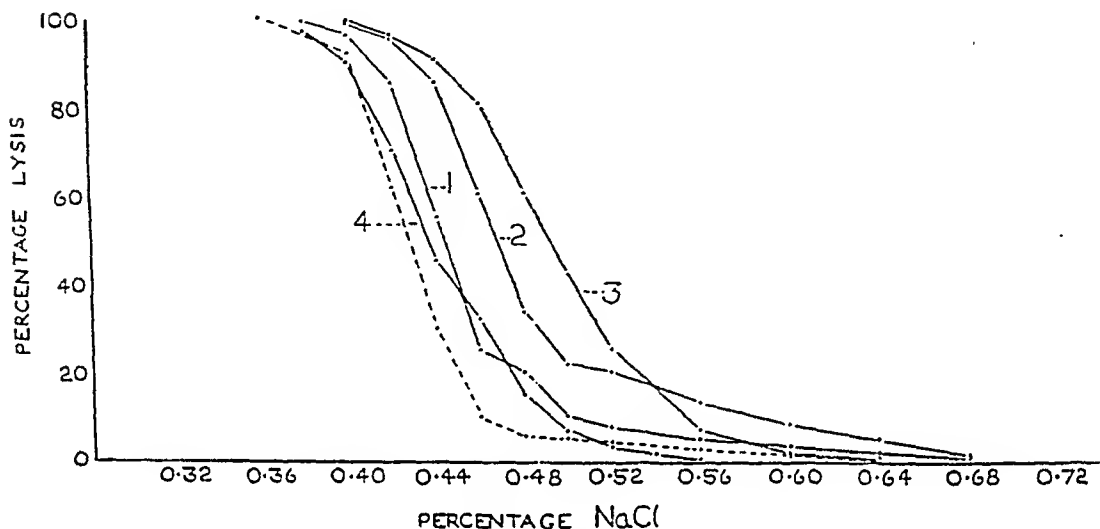


FIG. 6. Quantitative fragility curves from Case 7, showing the changes produced by splenectomy. Interrupted line = before anaesthetization. Continuous lines = (1) after induction of anaesthesia, (2) at completion of operation, (3) 24 hours later, and (4) five days after splenectomy.

a reduction in the point of 2 per cent. lysis from 0.58 per cent. to 0.50 per cent. saline.

There appear to be two possible explanations for the increase in resistance of the erythrocytes after splenectomy, both of which may be operative. Firstly, the removal of an organ which increases the fragility of the cells which circulate through it; it is well established that the fragility of erythrocytes taken from the splenic vein is greater than those of peripheral venous blood (MacAdam and Shiskin, 1922; Campbell and Warner, 1925; Gripwall, 1938); secondly, that as a consequence of the removal of the spleen and the resulting diminution in the rate of cell destruction, the bone marrow produces less fragile cells. The ultimate increases in resistance observed in all the cases in the present series except Case 9 can be accounted for on either basis, but the transient increases observed during the first 24 hours are not so easily explained (Fig. 6). It is possible that this may have been due in part to the effects of the anaesthetic employed (nitrous oxide, oxygen, and ether). Leake, Baekus, Burch, and O'Shea (1927) have claimed that in dogs ether anaesthesia for 30 minutes or more causes an increase in fragility, but no information on its effect in man appears to be available. In a control series

of observations on patients undergoing abdominal operations, including two cases of splenectomy, one for splenic enlargement of uncertain origin (later shown to be due to lymphadenoma) and the other for fibrocongestive splenomegaly (Banti's disease), I have found small increases. The average increase in median fragility between the samples withdrawn immediately before the commencement of anaesthesia and at the completion of the operation was 0.007 per cent. saline in the seven controls and 0.03 per cent. in three cases of familial haemolytic anaemia. It is likely that much of this increase is due to the anaesthetic causing splenic contraction and the expulsion of fragile blood into the peripheral circulation, and in the case of splenectomy to manipulation and compression of the spleen during removal. Indirect evidence that this occurs is provided by studying the changes in erythrocyte count during the course of the operation. Figures obtained from Case 7 show that before induction of anaesthesia, erythrocytes were 4,100,000 per c.mm., after induction 4,600,000 per c.mm., and after completion of operation 5,400,000 per c.mm. It is possible that a reduction in plasma-volume caused by anaesthesia (Gibson and Branch, 1937) is responsible for part of the sudden rise in erythrocyte count, and that fragility is slightly increased owing to the same mechanism causing a rise in plasma osmotic pressure. Doan, Curtis, and Wiseman (1935) who observed rises of 1,000,000 erythrocytes per c.mm., or more, at the completion of splenectomy in 14 cases of familial haemolytic anaemia, and studied the accompanying changes in blood-volume in at least one patient, concluded that a reduction in plasma-volume plays but a small part in causing the striking increase in erythrocyte count. In the case which they reported in detail the erythrocyte volume increased from 412 c.c. to 744 c.c. at the completion of the operation; the relative change in plasma-volume was much smaller, 4270 c.c. to 3900 c.c.

The effect of anaesthesia acting either directly or indirectly cannot be entirely responsible for the transient increases in fragility resulting from splenectomy. In two of the three patients where data are available (Cases 5, 6, and 7) a further increase in fragility was found 24 hours after operation, as compared with that of samples taken immediately after the operation had been completed. It is suggested that this is due to a temporary accumulation of unusually fragile cells which previously had been selectively removed from the circulation because of an increased susceptibility to the haemolytic action of the spleen.

The effect of splenectomy upon the shape of the fragility curve has rarely been reported, although most of the authors (see below), who have noted a decrease in fragility report a diminution in the limits between which haemolysis occurs. Waugh and Lamontagne (1940) describe one case in which splenectomy was followed by the loss of a 'tail' of fragile cells without a shift in the curve as a whole.

The effect of splenectomy upon the saline concentration at which lysis is first perceptible (initial lysis or minimum resistance) has been more frequently studied and it is generally agreed that although increased fragility persists

the cells usually become less fragile after removal of the spleen, but many of the reports are based on very few observations and are thus of limited value. The after-history of the patient whose spleen was removed by Spence Wells in 1887 (quoted by Dawson, 1931), in whom increased fragility was found 40 years after splenectomy, suggests that the increase is permanent, although this is the only case reported of such long duration.

Meulengracht (1922) reviewed the early literature and found that although a reduction in fragility seemed to be the rule the point at which lysis commenced remained higher than normal. Decreased but still abnormal post-operative fragility has been reported by Meulengracht (1922) in five cases, but it is interesting to note that if his figures given for 'hälbe' haemolysis are compared, only one case showed a significant reduction; Whiteher (1925) reported a reduction in two cases, MacAdam and Shiskin (1922) in one of three cases, Campbell and Warner (1925) in four cases, Dawson (1931) in five cases, Beekman and Jäderholm (1931) in three of four cases, Joyce and Mills (1932) in one of three cases, Barber (1934) in four cases, Doan, Wiseman, and Erf (1934) in about half of an unspecified total of cases, Doan, Curtis, and Wiseman (1935) in one case, Paxton (1935) in four cases, Vaughan (1937) in eight of 11 cases, Gripwall (1938) in three of four cases, and Haden (1939) in five of seven cases.

A return to normal fragility was described by Thursfield (1914) in one case, Doan, Wiseman, and Erf (1934) in one case, and Walkling (1931) in one case.

Fragility unaltered by splenectomy is reported by Dawson (1931), Whiteher (1925) in one of three cases, Joyce and Mills (1932) in one of three cases, Vaughan (1937) in one of 11 cases, and Gripwall (1938) in one of four cases. Daland and Worthley (1934) reported increased resistance in three patients, one, two, and five years after splenectomy, and a fluctuating value, not significantly different from the pre-operative level, in a further case.

Increase in fragility after splenectomy has been reported by Creed (quoted by Dawson, 1931) in one case, Vaughan (1937) in two of 11 cases, and Haden (1939) in two of seven cases, and transient increases by Thomson (1933) in one case, Doan, Wiseman, and Erf (1934) in one case, MacAdam and Shiskin (1922) in two of three cases, and Campbell and Warner (1925) in one of four cases.

The histopathology of the spleen in familial haemolytic anaemia. The histological appearances of the spleen in familial haemolytic anaemia are well known, and the descriptions of authors such as Eppinger (1920), Meulengracht (1922), McNee (1931), Thompson (1932), Turnbull (1936), and Klemperer (1938) are in general agreement. The essential features are as follows: the pulp of the spleen is distended with erythrocytes; the sinuses are small but prominent, with the lining endothelial cells easily seen and their nuclei often protruding into the lumina; neither erythrophagocytosis nor hyperplasia of the reticulum cells of the pulp is usually obvious, but Klemperer (1938) believes that the latter may be masked by the congestion;

iron-containing pigment is present in unusual amounts and fibrosiderotic nodules are often found. Engorgement of the spleen is, therefore, the most striking abnormality, and it has been assumed that this facilitates or engenders erythrocyte destruction (Eppinger, 1920; Gripwall, 1938; Fåhræus, 1939), but the way in which the congestion is produced is not known. Eppinger (1920) thought that hyperaemia was due to primary arteriolar and capillary vasodilation, but Klemperer (1938) suggested that it was secondary to the presence of pathological erythrocytes, although he expressed no opinion as to the mechanism. Whipple (1941) believes that the shape of the spherocytes interferes with their passage through the stomata of the venous sinuses, and so causes distension of the pulp spaces, which compresses the venous sinuses and narrows their stomata, so setting up a vicious circle.

It was hoped that a clue to the mechanism of congestion might be obtained by experiments with excised spleens. The possibility that direct pathways from capillary to sinus were absent or deficient was investigated by timing the passage of test objects perfused through the spleen at a constant pressure (100 mm. of mercury). Cannulae were inserted into a suitable artery and its associated vein, and the preparation perfused with saline; as soon as the circulation was established 5 c.c. of a 5 per cent. suspension of fowl's cells was rapidly injected into the arterial cannula and the efflux from the vein collected at intervals and examined for the presence of large oval fowl erythrocytes. In six control spleens (five from post-mortems and one from operation) the fowl's cells appeared in the efflux 3 to 5 seconds after injection into the arterial cannula, compared with 4 to 5 seconds in three spleens from cases of familial haemolytic anaemia. These results indicate that the spleen in familial haemolytic anaemia has capillary to sinus pathways as direct as in the normal. In spite of this it is difficult to free the spleens from blood by perfusion with saline. After 20 minutes' perfusion at 100 mm. of mercury the pulps of nine control spleens (three removed at operation and six at post-mortem) were practically free from erythrocytes. On the other hand when seven spleens from cases of familial haemolytic anaemia were perfused, relatively few erythrocytes were removed from the pulp in 20 minutes, and in two cases large numbers were still present even after 100 minutes' perfusion. These observations on the excised organ support the view that there is *in vivo* stagnation of blood in the spleen in familial haemolytic anaemia, and suggest that much of the pulp may be a backwater outside the main current of the blood-stream.

The exact location of the blood within the living spleen in familial haemolytic anaemia is another unsolved problem. Knisely (1936) claimed that direct inspection of the spleen in anaesthetized animals (mice, rats, and cats) showed that, contrary to the generally accepted view, all the blood was contained in the sinuses, and concluded that erythrocytes were found in the pulp only after manipulation of the spleen or the death of the animal. These conclusions have since been disputed by MacKenzie, Whipple, and Wintersteiner (1940) using a similar technique, but in support of

Kniscly's views Gripwall (1938) has claimed that small pieces of two spleens rapidly fixed in Susa's fluid showed the sinuses to be well filled with blood instead of being compressed by a distended pulp. This problem needs further investigation.

The Pathogenesis of Familial Haemolytic Anaemia.

The pathogenesis of familial haemolytic anaemia has been extensively discussed in recent years, particularly by Meulengracht (1938), Lloyd (1941), and Dameshek (1942), but no completely satisfactory solution has been advanced. One of the important characters of the disease is 'spherocytosis', that is, the presence in the peripheral blood of erythrocytes of smaller diameter but greater thickness than normal. The more spheroidal shape of the cell is generally accepted as the cause of the increased fragility to hypotonic saline, and the view that an abnormality of the erythrocyte was the primary cause of the disease has had many adherents, including Naegeli (1931), Haden (1934, 1940), Thompson (1936), Vaughan (1936), Gripwall (1938), and Lloyd (1941). Recent work has demonstrated that in addition to their spheroidal shape the erythrocytes in familial haemolytic anaemia are abnormal in other ways. They are more easily broken up by lysolecithin than normal cells (Gripwall, 1938; Singer, 1940; Lloyd, 1941), and undergo autohaemolysis rapidly *in vitro* both before and after splenectomy (Ham and Castle, 1940; Dacie, 1941; Lloyd, 1941). Transfusion into healthy recipients of blood from patients with familial haemolytic anaemia has shown that the cells have a shorter life than normal (Lloyd, 1941; Dacie and Mollison, 1943), whereas healthy cells have a normal survival time when transfused into patients with familial haemolytic anaemia (Dacie and Mollison, 1943).

While it is established that the erythrocyte in familial haemolytic anaemia is abnormal in shape and behaviour, the question whether these abnormalities represent a primary disturbance of erythropoiesis or are due to the action of an abnormal haemolytic agent or mechanism has not been settled. The first hypothesis is attractive and difficult to refute, but there is much indirect evidence in favour of the latter view. Spherocytosis and increased fragility have been recorded in a number of other diseases, for example acute haemolytic anaemia (Dameshek and Schwartz, 1938a), myelosclerosis and allied syndromes (Vaughan and Harrison, 1939; Weil and Perlès, 1938), leukaemia (Heilmeyer, 1936; Singer, 1940), erythroblastosis foetalis and normal foetuses *in utero* (Hampson, 1928), carcinomatosis of bones (Waugh, 1936; Lucey, 1936), lymphadenoma (Davidson, 1932; Singer, 1936; Creed, personal communication), and in my own experience I have demonstrated increased fragility in each of the above conditions (unpublished observations). Further examples occurring in haemolytic anaemia associated with an ovarian dermoid cyst, lymphosarcoma of the pancreas, lymphadenoma, lymphatic leukaemia, and pneumonia have been recently reported by Singer and Dameshek (1941). The presence of spherocytes or increased fragility

resulting from the administration of haemolytic immune sera to experimental animals has been reported by Banti (1913), Pearce, Krumbhaar, and Frazier (1918), Dameshek and Schwartz (1938*b*), and Tigertt and Duncan (1940); haemolytic poisons such as toluyldiamine (Eppinger, 1920), arsine (Kicse, 1937), and acetylphenylhydrazine (Cruz, 1941) cause similar changes. In man spherocytes and increased fragility have been observed in haemolytic anaemia caused by acetylphenylhydrazine (Creed and Dacic, unpublished observations) and sulphanilamide (Ham and Castle, 1940; Gilligan and Kapnick, 1941).

Unfortunately, experimental studies have not solved the mechanism of spherocyte production. The hypothesis that spherocytosis is due to direct action of a lytic agent upon erythrocytes is not supported by *in vitro* experiments. It is known that neither immune sera (Banti, 1913; Ham and Castle, 1940), toluyldiamine (Eppinger, 1920), nor sulphanilamide (Emerson, Ham, and Castle, 1941) cause increased fragility or spherocytosis *in vitro*, and direct observation of the haemolysis by complement and immune serum of human erythrocytes showed that after passing through a crenated stage the cells assumed a spheroidal form for a few seconds only before haemolysis occurred (unpublished personal observations). The possibility that haemolytic poisons which are inactive *in vitro* may give rise to metabolites which cause spherocytosis and haemolysis receives strong support in the recent work of Emerson, Ham, and Castle (1941). They showed that oxidizing agents derived from substances such as sulphanilamide caused increased fragility and ultimate haemolysis *in vitro* and severe haemolytic anaemia with a great increase in fragility on injection into cats. Striking differences exist between the *in vivo* and *in vitro* action of haemolytic sera. Muir and McNee (1911) showed that such sera were far more active *in vivo* than *in vitro* under optimum conditions. Banti (1913), who was aware of Muir and McNee's work, produced evidence that the haemolytic agents which he studied (immune serum and phenylhydrazine) were potentiated by the spleen and reticulo-endothelial system by showing that haemolysis was less severe and there was less increase in fragility in splenectomized animals. A possible explanation for these observations is found in the work of Ham and Castle (1940) who suggested that the haemolytic anaemia produced by immune serum is mainly caused by its content of agglutinins and is only in part due to haemolysin. The presence of agglutinates is considered to cause intravascular stasis with consequent haemolysis, particularly within the spleen.

It is clear, therefore, that exogenous haemolytic agents can produce spherocytosis *in vivo* and although this in no way disproves the hypothesis that the production of spherocytes is the primary abnormality in familial haemolytic anaemia, it at least suggests the possible presence of an endogenous haemolytic agent. Dameshek and Schwartz (1938*b*) suggested that a haemolysin of the immune body type might be responsible and that failure to demonstrate it might be due to its fixation on to erythrocytes.

Certain other possible mechanisms of spherocyte production merit brief

discussion. Meulengracht (1938) suggested that spherocytosis might be a regeneration phenomenon, but this view has been rendered untenable by the subsequent demonstration that the appearance of spherocytes in experimental haemolytic anaemia precedes the rise in reticulocytes (Dameshek and Schwartz, 1938b), and by the absence of significant spherocytosis in some forms of chronic haemolytic anaemia in man, such as the Marchiafava-Micheli syndrome (Ham, 1939). Lüdke (1918) claimed that autohaemolysins and increased fragility could be produced in dogs by bleeding and re-injection of the blood after lysis with distilled water. I have repeated this experiment in rabbits and guinea-pigs, but have been unable to produce significant alterations in fragility in either animal (unpublished observations).

The spleen undoubtedly plays an important part in the natural history of the disease, but the persistence of abnormal cells after its removal demonstrates that it alone is not responsible for the abnormalities. Possibly the spleen acts in conjunction with the rest of the reticulo-endothelial system, but there is no proof of this. It has been suggested (Gripwall, 1938; Lloyd, 1941) that the enlargement of the spleen may be the result of the increased demands on its haemolytic function caused by the presence of abnormal cells. Removal of the spleen is apparently sufficient to reduce the rate of haemolysis to limits which can be satisfactorily compensated. The scanty data on pigment excretion (Watson, 1937; Barker, 1938; Singer, Miller, and Dameshek, 1941) suggest that the rate of haemolysis then becomes entirely normal. Further evidence is required on this point in view of the persistence of cellular abnormalities in familial haemolytic anaemia, and evidence is also required as to the distribution and activity of haematopoietic bone marrow after removal of the spleen. It is generally believed that the reticulocyte level falls to normal after splenectomy, but there are sufficient reports in the literature to suggest that this may not be strictly true² and consequently that the rate of cell destruction may not always be reduced to normal. Thompson's (1939) case where a fatal relapse was found to be due to multiple spleniculi is an interesting and rare example of failure of splenectomy.

The mechanism of haemolysis within the spleen is not yet clearly known. Erythrophagocytosis is generally inconspicuous, indicating a humoral rather than a cellular mechanism. Recent authors (Gripwall, 1938; Fåhræus, 1939; Lloyd, 1941) have attributed haemolysis to the action of lysolecithin

² Reticulocyte counts above 3 per cent. have been noted months after splenectomy by Pemberton and Mahorner (1931), Gripwall (1938), Thompson (1939), Lloyd (1941), and Singer, Miller, and Dameshek (1941). Thompson's and Lloyd's series are the largest. Lloyd found fluctuations between 1.3 per cent. and 3.1 per cent. in four of 15 patients, and Thompson 2.1 per cent. to 8.7 per cent. in 12 of 23 patients.

In six of 12 patients in my own series seen between three months and six years after splenectomy the counts ranged from 1.5 to 3.6 per cent. (excluding doubtful cells with a single dot of reticulum). In a further patient of doubtful pathogenesis (Case 8) 8 per cent. of reticulocytes were present 23 days after operation and 3.7 per cent. three years later.

(see Bergenhem and Fåhræus, 1935 ; Bergenhem, 1939) produced in excessive quantities by a spleen in which an unusual degree of circulatory stasis was assumed to occur, and the recent claims of Gripwall (1938), Singer (1940), and Lloyd (1941) that the erythrocytes in familial haemolytic anaemia are unusually sensitive to the haemolytic effect of lysolecithin appear to fit in with these ideas. Ham and Castle (1940) believe that circulatory stasis of a normal degree acting upon cells which are unusually susceptible to its effects is sufficient to account for the increased haemolysis. The observation that healthy erythrocytes appear to have a normal span of life when transfused into patients with familial haemolytic anaemia (Dacie and Mollison, 1943) is at first sight in accord with Ham and Castle's conception. Study of the histology of the spleen shows, however, that in these patients the organ is greatly engorged with blood. It is difficult to reconcile the finding of a congested spleen in which the blood is presumably stagnant with the normal survival of healthy cells after transfusion, and at the same time accept Ham and Castle's hypothesis that intravascular stasis engenders haemolysis. A possible solution is given by the hypothesis that stagnation is selective ; whilst normal discoidal cells have no difficulty in traversing the spleen, spherocytes, possibly because of their spheroidal shape, are unable to pass through the stomata of the splenic sinuses (see Whipple, 1941).

The last points to consider are the significance of the histopathology of the spleen and whether similar appearances are found in other disorders. Although engorgement with blood is invariably found in familial haemolytic anaemia it is becoming increasingly clear that it is not specific for this disease. Dameshek and Schwartz (1940) collected histological reports on 29 spleens from patients considered to have acute haemolytic anaemia ; in 12 pulp congestion was the predominant pathological change. All, except Case 8 of Davidson and Fullerton (1938), showed a considerable increase in fragility. It is admittedly difficult to distinguish between familial haemolytic anaemia in crisis and acute haemolytic anaemia, but in certain of the patients, at least, the diagnosis appears to be unassailable ; those of Rosenthal and Corten (1937) and Troisier and Cattani (1932) showed autohaemagglutination, and haemolysins of the immune body type were demonstrated in the patients of Dameshek and Schwartz (1938*a*). Moreover, marked spherocytosis in the peripheral blood and intense vascular congestion of the spleen are produced by the administration of haemolytic sera or poisons to laboratory animals (Banti, 1913 ; Eppinger, 1920), and similar changes have been noted in man in acute haemolytic anaemia due to sulphanilamide (Fox and Ottenberg, 1941). The interpretation of these facts is not known. It seems that splenic congestion is a reaction of uncertain mechanism produced by the presence of haemolytic substances whose activities are thereby potentiated. Further work is necessary to determine the respective parts played by the haemolytic agent itself, metabolites derived from it, congestion of the spleen and of other parts of the reticulo-endothelial system, and the reticulo-endothelial cells themselves in the genesis of the haemolytic anaemias due

to haemolysins or haemolytic poisons, but although the details of the process are unknown the proved inter-relationship between haemolysins, spherocytosis, and splenic congestion should stimulate search for a possible haemolytic agent or abnormal metabolic product in familial haemolytic anaemia.

Summary

1. Erythrocyte fragility to hypotonic saline was studied in 24 patients with familial haemolytic anaemia (acholuric jaundice). Three main types of quantitative fragility curves could be distinguished—'tailed' curves (12 cases), 'diagonal' curves (6 cases), and 'normal type' curves (5 cases).

2. Splenectomy was performed on 12 patients in 11 of whom resistance to haemolysis was increased after operation. In seven patients with 'tailed' curves increase in resistance was preceded by a transient post-operative increase in fragility. In one patient, first seen in a haemolytic crisis, fragility ultimately became normal; in another there was an increase in fragility compared with the pre-operative level, which persisted for at least three years after splenectomy.

3. The histopathology of the spleen was studied in 12 cases. Great engorgement with blood was the most notable feature. Perfusion experiments with excised spleens failed to demonstrate the cause of the congestion. Although it was found to be difficult to free the pulp from blood by perfusion with saline, the time of circulation of test objects (fowl erythrocytes) through the spleens appeared normal.

4. The various theories on the pathogenesis of the disease are considered. The available evidence suggests a haemolytic disorder based upon the presence of erythrocytes with an increased tendency to haemolysis. Although there is much evidence to support the view that this represents a primary defect in erythropoiesis, experimental and clinical observations on the relationship between haemolytic anaemia, splenic congestion, and spherocytosis indicate that the possibility of the presence of an abnormal haemolytic agent or metabolite cannot be ignored.

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THE TONSIL-ADENOID OPERATION IN RELATION TO THE HEALTH OF A GROUP OF SCHOOLGIRLS¹

By J. H. P. PATON

In a previous paper figures were published showing a high rate of operation on tonsils (43 per cent.) among the girls of a large boarding school (Paton, 1928). Although the operation is known to confer great benefit in carefully selected cases, no advantage was evident in the group of those operated on when compared with the others. It was suggested that such an operation rate was unnecessarily high. Since that date various writers have urged more careful selection of those subjected to the tonsil-adenoid operation (Glover, 1938; Medical Research Council Rept., 1938). Being in possession of records for a further period of 10 years I undertook the present inquiry to determine the frequency of operative interference with tonsils and adenoids, and the relation of that interference to the health of those concerned.

The records of 909 girls admitted to the boarding school referred to between 1930 and 1939 are dealt with. The girls are recruited from well-to-do families, and are healthy on admission, that is to say, no girl suffering from chronic ill health or severe disability is admitted to the school. The majority enter school at or about puberty. The data are extracted from the history and state of health on examination recorded at entry, and the records of illness during school years.

Records Obtained on Admission to School

Frequency of tonsil-adenoid operations. From Table I it is seen that 57 per cent. of the girls had had tonsils removed, as compared with 43 per cent. in the 1928 series, and 50 per cent. had had adenoids removed. The operation rate has considerably increased, and more than half of the girls had

TABLE I

*Frequency of Tonsil and Adenoid Operations among 909 Girls admitted to
School between 1930 and 1939*

Operation (516 girls)		No operation (393 girls)	
Tonsils and adenoids removed	435 = 48 %		
Tonsils only	57 = 6 %	393 = 43 %	
Adenoids only	24 = 3 %		
Total	= 57 %	Total	= 43 %

When tonsils were removed at one operation and adenoids at another the case is included in the tonsil and adenoid group.

¹ Received October 9, 1942.

undergone one operation or another before entering the school. In the series, 26 girls had had operation repeated, in one instance on three occasions.

Recurrence after operation. Regrowth of tonsillar tissue undoubtedly occurs occasionally. In Case 791, for example, when examined three months after a tonsil-adenoid operation, the left tonsil extended beyond the posterior pillar of the fauces and the right considerably farther. Regrowth is probably, but by no means certainly, impossible if the mucous lining of the tonsillar fossa is completely replaced by scar tissue. As will be seen below, more than a third of those whose tonsils had been operated on showed remnants.

State of tonsils on examination. The apparent size of the tonsils was recorded in all cases. Tonsillar tissue was visible in 40 per cent. of the

TABLE II

		Visibility of tonsillar tissue					
		0	L ¹	L ²	L ³	L ⁴	L ⁵
492	Tonsil operation	60 %	32 %	5 %	1 %	2 %	0
417	No tonsil operation	5 %	16 %	40 %	25 %	13.5 %	0.5 %

0 = tonsil not visible. L¹ = just visible. L² = extending halfway to posterior pillar of fauces. L³ = extending to edge of posterior pillar. L⁴ = beyond posterior pillar. L⁵ = touching uvula.

The larger tonsil is recorded in all cases.

operation cases and in 95 per cent. of the others. The larger tonsil extended beyond the posterior pillar of the fauces in 2 per cent. of the operation cases and in 14 per cent. of those not operated on. If we regard a tonsil which extends to the posterior pillar or beyond it as 'abnormally large' we find such 'large' tonsils in 3 per cent. of the operation cases and in 39 per cent. of the remainder. Such a division is, of course, arbitrary, and there is no evidence that size alone is any criterion of the health or disease of a tonsil.

The relation of the operation to health, as recorded on admission to school.

State of the anterior cervical glands. One of the most conclusive proofs of chronic disease of the tonsil is afforded by secondary enlargement of anterior cervical glands. The state of those glands was recorded in all cases, and the presence of scars in the neck, since this indicates a previous lymphadenitis, was also noted. Unfortunately the dates of gland operations were not recorded, so that it is not known whether they preceded or followed tonsillectomy. In this section of the inquiry I have included in 'operation cases' only those in whom tonsils had been removed.

Chronic cervical adenitis, though it may be arrested by removal of the tonsil, is not likely to subside completely, and some palpable trace of it will remain. Its total incidence may therefore be determined with near accuracy, if the scar rate is added to the rate of gland enlargement found on examination. When this is done it is seen that the incidence of chronic lymphadenitis was the same among the tonsillectomized as among the non-tonsillectomized. Neck scars were, however, more frequent in the group whose tonsils had been removed. This suggests that, in the first instance, the number of cases of severe lymphadenitis was greater in this group, and that in fact the presence

of chronically enlarged glands was the indication for the tonsil operation. It is evident from Table III that this could not have been the indication in more than 4 per cent. of the tonsillectomies performed. Definite glandular enlargement was commoner among the non-tonsillectomized. It was not present in more than 5 per cent., and the enlargement was never gross. It

TABLE III

Presence of Palpable or Enlarged Anterior Cervical Glands

No. of cases		Glands					
		0	L ¹	L ²	L ³	L ⁴	Scar
492	Tonsil operation	76 %	17 %	2 %	1 %	0	4 %
417	No operation	75 %	18 %	4 %	1 %	0	2 %

enlarged

0 = glands not palpable. L¹ = just palpable. L² = palpable.
L³ = enlarged. L⁴ = much enlarged. Scar = scar in neck.

was noted in 3 per cent. of those tonsillectomized. Finally it may be noted that the proportion showing 'no palpable glands' was almost the same for the tonsillectomized (76 per cent.) as for those in whom no operation had been performed (75 per cent.); while if glands 'just palpable' are considered normal (as they may well be), a normal state of the glands was found in 93 per cent. of the operation cases and in 93 per cent. of the remainder.

History of otorrhoea. In this section only those whose adenoids had been removed are included in the operation group. The occurrence of otorrhoea

TABLE IV

Relation of Tonsil and Adenoid Operation and Adenoid Operation to Otorrhoea.
Operation Cases

Operation	No. of cases	Otorrhoea	Per cent.	Relation to tonsil and adenoid operation	No. of cases
Tonsil and adenoid operation	435	54	12	Before tonsil and adenoid operation	22
				After tonsil and adenoid operation	19
				Before and after tonsil and adenoid operation	2
				Dates not recorded	11*
Adenoid operation	24	2	8	Before adenoid operation	1
				After adenoid operation	1
Tonsil operation	57	5	9	Before tonsil operation	0
				After tonsil operation	3
				Dates not recorded	2
Total operations	516	61	11	—	—

Non-operation Cases

No operation	393	26	6.6	—	—
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* Five of these 11 cases were recorded as having the tonsil and adenoid operation and otorrhoea in the same year. In some the operation may have followed the otorrhoea; in others otorrhoea may have developed during convalescence from the operation, not an uncommon sequence.

in the series and, in most cases, the time relation between adenoid operation and the onset of otorrhoea, is shown in Table IV.

Removal of adenoids is commonly advised in cases of recurrent ear-ache, with the hope of preventing subsequent attacks and so guarding against the future development of otorrhoea. In 20 of 43 cases in which the relative dates were recorded the initial attack of otorrhoea occurred subsequent to an adenoid operation. The operation did not in these cases prevent it. Nor

TABLE V

Periods which Elapsed between Tonsil and Adenoid Operations and the Development of Otorrhoea

Years	1	2	3	4	5	6	7	10
Cases	2	3	5	4	4	2	2	1

is recurrence of otorrhoea always prevented by the removal of adenoids. Of five cases of recurrent otorrhoea in which adenoids were removed, subsequent relapses occurred in four. The following case is an example. A girl had the tonsil and adenoid operation at 9 years. She gave a history of attacks of otorrhoea at 3, 9, and 13 years. Glover and Griffith (1931) mention that adenoidectomy does not appear to reduce the probability of a future attack of mastoiditis. Nine girls in the present series gave a history of a mastoid operation. In five of these adenoids had been previously removed.

History of rheumatism. Twelve girls in the series gave a history of true rheumatism, that is to say of subacute rheumatism or rheumatic fever as recorded by their family doctors. Four had had no tonsil or adenoid operation and in two who had had the tonsil and adenoid operation the relative dates of the rheumatic attack and the operation were not recorded. In six of the 12 cases tonsils had been removed (tonsil and adenoid operation, 4; tonsil operation, 2) before the initial attack of rheumatism.

Effect of the tonsil-adenoid operation on growth. It is undoubted that when malnutrition is present as a result of tonsillar disease, tonsilleectomy will be

TABLE VI

Weights in Group at Ages 13 and 14 Years

Age	No. of cases	Under 100 lb.	100 to 120 lb.	120 to 140 lb.	140 to 160 lb.	Above 160 lb.
13 Operation	272	24 %	51 %	23 %	1 %	1 case
No operation	210	33 %	46 %	17 %	4 %	1 case
14 Operation	178	15 %	49 %	30 %	7 %	No cases
No operation	135	10 %	51 %	35 %	5 %	No cases

followed by considerable improvement. The following is the history of such a case. In July 1933 a tonsil-adenoid operation was done, the septum was cauterized, and the uvula shortened. On admission to school in September 1933, this girl weighed 81 lb. During the Autumn Term she developed otorrhoea (her first attack) from which she made a good recovery. In July 1934 her weight was 94½ lb., a gain of nearly a stone in 10 months. Some authors believe that increased growth always follows a tonsil-adenoid operation, and even surmise that the tonsils have an inhibitory effect upon growth. There is no evidence supporting this view in my series. An analysis of the

heights and weights of the 909 girls examined showed no significant difference between the tonsillectomized and the others. Table VI shows the weights for the girls of 13 and 14 years.

Girls of exceptionally low weight and height were as common among the tonsillectomized as among the others. Thus, of girls below 60 in. in height, 47 had been operated on and 39 had not; while of those under 90 lb. weight 31 had had tonsils removed and 34 had not. Girls above the average weight were as common among the tonsillectomized as among the rest.

Incidence of Illness Among 909 Girls from 1930 to 1939

It is to be noted that the records are unsatisfactory in one respect, namely, that while those entering the school in the first years of the decade were observed throughout their whole school course, those admitted in the last few years were not. Those entering in 1939, for example, were only observed for a fraction of that year, and those entering in 1938 for one year and a fraction. It is believed that in spite of this the figures obtained give a fair cross section of the illness in the group during the period. A rule of the school is that no girl who is unable to attend school on any day is permitted to remain in her boarding house. She is at once removed to the sick house where her disability, however slight, is recorded, and where she stays until she is able to return to school.

Admissions to the sick house from all causes are summarized in Table VII. It is evident that the loss of school time from illness was rather greater,

TABLE VII

Attacks of Illness from All Causes in 909 Girls from 1930 to 1939

Operation	Girls	Admissions	Days lost	Admissions per girl	Days lost per girl
Tonsil and adenoid operation	435	1,668	9,001	3.8	20.6
Tonsil operation	57	206	1,051	3.6	18.4
Adenoid operation	24	66	362	2.7	15.0
All operations	516	1,940	10,414	3.7	20.1
No operation	393	1,322	7,293	3.3	18.5

certainly not less, among the girls who had been subjected to operation, but it must be noted that this is not true of the small group of girls in whom adenoids alone had been removed. They lost on the average three days less than any of the other groups while at school. In view of their small number, 24 only, it is doubtful whether much significance can be attached to the figures. The point will be referred to again in connexion with special diseases.

Admissions from special illnesses. Certain diseases having a possible association with tonsils or adenoids were selected for special consideration, and are shown in Tables VIII and IX.

Tonsillitis. No case of quinsy occurred during the decade; 'tonsillitis', therefore, refers only to 'follicular or lacunar tonsillitis'. The disease was rare in the period and never reached epidemic prevalence. The incidence

was about five times as great among those in whom no operation had been done as among the tonsillectomized. Glover and Wilson (1932) found a similar trend, though in their series the divergence in favour of the tonsillectomized was less than in the present series. Several epidemic outbreaks

TABLE VIII

Admission rate per 100 Girls for Pharyngitis, Tonsillitis, Adenitis, Ear-ache, and Otorrhoea in 909 Girls

Disease	Operation			No operation (393 girls)
	Tonsils and adenoids (435 girls)	Tonsils only (57 girls)	Adenoids only (24 girls)	
Pharyngitis	40 %	53 %	54 %	41 %
Tonsillitis	1 %	2 %	4 %	5 %
Acute adenitis	3 %	5 %	0	2 %
Ear-ache	8 %	2 %	0	8 %
Otorrhoea	1 %	0	8 %	0.5 %

TABLE IX

Admission rate per 100 Girls for Certain Other Diseases

Disease	Operation			No operation (393 girls)
	Tonsils and adenoids (435 girls)	Tonsils only (57 girls)	Adenoids only (24 girls)	
Colds	114 %	112 %	71 %	97 %
Influenza	43 %	33 %	33 %	39 %
Bronchitis	27 %	23 %	4 %	16 %
Pneumonia	0.4 %	0	0	0.2 %
Pleurisy	0.2 %	0	0	0

It is to be observed that the incidence shown is not annual incidence. It represents the admissions per cent. of these 909 girls during the years they remained in the school.

were included in their figures. The removal of adenoids alone was not accompanied by an apparent reduction in the incidence of tonsillitis.

Pharyngitis, which includes all other cases of sore throat, was as common among the tonsil-adenoid operation group as among those who had had no operation, but not more common. The reduction in tonsillitis after tonsillectomy referred to in the previous paragraph was not, that is to say, accompanied by a corresponding increase in sore throat from other causes; it was a true reduction. An apparent increase in the pharyngitis rate is shown among those who had had tonsil operations only, and also among those who had had adenoid operations only. These anomalous results serve to show that, as was indicated earlier, too much reliance must not be placed on percentages calculated from such small numbers.

Acute adenitis was more common among those in whom tonsils had been removed. Davis (1938) believes that acute cervical adenitis is common and more severe in tonsillectomized patients.

Ear-ache and otorrhoea. If adenoidectomy protects against ear-ache and otorrhoea, the incidence of otitis media among those who have had adenoids removed should be reduced, but this is not so. The incidence of ear-ache was about the same in the tonsil and adenoid operation group as for others,

but the number of cases of otorrhoea was greater. A much greater increase in otorrhoea was noticeable in the group in which adenoids alone were removed. Of the seven cases of otorrhoea, five had had adenoids already operated on. Further, of the 24 girls who had had the adenoid operation alone, two developed otorrhoea at school, while among 450 whose adenoids had not been operated on, only two cases of otorrhoea occurred. It should be noted that one of the unusual features in this decade was the low prevalence of otitis media, possibly associated with the low incidence of tonsillitis during the same period, similar infections being responsible for both.

To this account may be added an analysis which was made some years ago of 56 cases of otitis media collected from school records. These were

TABLE X

Cases of Otitis Media from School Records in Relation to Tonsil and Adenoid Operation

	Group			
	A	B	C	D
Total cases	18	8	8	22
Tonsil and adenoid operation	7	4	6	10
Adenoid operation	1	—	—	—
Tonsil operation	1	—	—	3
No operation	9	4	2	9

Group A = Initial otorrhoea.

Group B = Recurrent otorrhoea.

Group C = Drum bulging.

Group D = Drum red only.

divided into four groups. Group A suffered from a first attack of otorrhoea at school, Group B from a recurrence, Group C showed some bulging of the drum from which complete recovery followed, and Group D showed redness of the drum only. The results are shown in Table X. More than half of these cases had already had adenoids removed.

Common colds were more frequent among the tonsillectomized in the present series. The Medical Research Council's Committee (1938) found that in a group of boys observed before and after tonsillectomy the incidence of influenza and nasopharyngeal infection was reduced in the period immediately following the operation, but they point out that the operation was done only in carefully selected cases.

Influenza. Operation did not reduce the susceptibility of the subject to this disease.

Bronchitis. The incidence of bronchitis was much greater among those whose tonsils had been removed, whether alone or in conjunction with adenoids. The removal of adenoids on the other hand appeared greatly to reduce the susceptibility to bronchitis, but again the small number of cases in the group throws doubt upon the result. The figures are so striking that they suggest that records in this respect of a large number of individuals who have had the adenoid operation only would be of interest.

Pneumonia and pleurisy were very rare, but were more common among the operation group.

Exanthemata. Measles, rubella, pertussis, chicken-pox, and mumps occurred in the school in the period under review. Of 516 operation cases 26 per cent. were affected, and of 393 non-operation cases 24 per cent. were affected, so the operation neither increased nor diminished susceptibility to those infections.

Discussion and Summary

The numbers dealt with are admittedly small, but it is believed that this disadvantage is outweighed by the fact that detailed records of each individual in the series are available. The group who had undergone the tonsil-adenoid operation and the group in whom no operation had been performed are sufficiently large and sufficiently similar in numbers to form a good basis for comparison.

Unfortunately those in whom tonsils alone or adenoids alone have been removed are so few in number that percentages based on them must be accepted with caution. Nevertheless the comparative incidence of certain ailments in the two groups is of value in assessing the respective effects of the tonsil or the adenoid factor in the combined operation. They are therefore detailed and are referred to when they appear to be significant. I believe that much light would be thrown on the subject if the outcome of such single operations was studied in large numbers of subjects.

The general figures support the opinion of the Medical Research Council Committee (1938) that there is a tendency 'for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result'. Those operated on, at any rate, show no advantage over the others as regards their state of health on admission to school, but it may be argued that as a group they were in the first instance below the normal standard of health, and that the operation was probably advised for that reason, with the result that their health, when they arrived at school, was as good as that of the others. No better result, it may be said, could be expected. It is impossible in the absence of detailed information to prove or disprove such an assumption. It is difficult to believe that it can apply to more than a minority of the 43 per cent. subjected to operation. This doubt is strengthened when it is found that as many girls of poor height and weight are found among the operation group as among the rest.

It was with this consideration in mind that a more detailed analysis of the illness affecting the two groups during their school years was undertaken. For, if the incidence of those conditions, for the relief or prevention of which operation is commonly recommended, is compared in the two groups, data are provided which indicate the effect of operation as regards future health.

Those in whom no operation had been done are taken as a control group, approximating to normal, and are used as the standard with which the combined operation group is compared. When this is done the following facts emerge:—

1. The operation group was no healthier than the control group on arrival at school.

2. The operation group was less healthy than the control group while at school. This is best shown by the number of school days lost through illness (Table XI).

TABLE XI

	Tonsil and adenoid operation (435 girls) Days lost	No operation (393 girls) Days lost
All illness	5,323	4,302
Respiratory affections, excluding pneumonia and pleurisy	1,666	1,223
{ Colds	1,566	1,187
{ Influenza	832	477
{ Bronchitis	39	210
{ Tonsillitis		

3. The operation group suffered less from tonsillitis.

4. The operation group suffered much more from respiratory infections, and lost more days from bronchitis alone than they gained in respect of tonsillitis.

5. When the small groups in whom a single operation was performed (tonsil operation, 57 cases; adenoid operation, 24 cases) are considered certain deductions are warranted.

(a) Removal of the tonsils is the factor in the combined operation responsible for the reduction in tonsillitis and for the increase in respiratory infections.

(b) Removal of adenoids appears to be followed by certain definite effects. Adenoidectomy alone reduces the liability to respiratory infections, but it is evident that in the combined operation group the removal of adenoids failed to counteract the increase in respiratory infections which resulted from the tonsillectomy. Removal of adenoids increases the liability to acute otorrhoea. The evidence, put forward in some detail, shows that recurrent attacks of otorrhoea are seldom prevented and primary attacks of otorrhoea are more frequent after the operation.

Conclusions

The figures put forward support the conclusion of Glover and Wilson (1932), arrived at from a survey of more than 14,000 records, that a large proportion of the tonsil and adenoid operations now done in children are 'unnecessary, entail some risk, and give little or no return'.

The figures also show that removal of tonsils increases the susceptibility to respiratory infections, and that the adenoid operation is followed by increased susceptibility to middle ear inflammation.

They corroborate Glover's (1938) assertion that a great reduction in the operation rate 'would be followed by no unsatisfactory result and, it may be, by actual benefit'.

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GALACTOSE TOLERANCE TESTS IN THYROTOXICOSIS¹

BY C. G. BARNES AND EARL J. KING

(From the Emergency Medical Service Medical and Pathological Services, Sector VI)

It has long been known that patients suffering from thyrotoxicosis have a diminished tolerance for glucose, for during standard glucose tolerance tests many such patients show hyperglycaemia and glycosuria. This lowered tolerance for glucose might have formed a suitable test for thyrotoxicosis, were it not that several factors besides absorption and storage of glucose affect the level of the blood-sugar. In particular, the effect of glycogenolysis from the liver under the influence of apprehension or excitement, changes in the rate of utilization of the sugar in the tissues, and variations in the renal threshold for glucose make the interpretation of the curve difficult.

It has been shown by Lichtman (1932) and Althausen and Wever (1937) that in thyrotoxicosis there is also a diminished tolerance for galactose. When this sugar is taken by mouth it is absorbed into the blood-stream and converted into glycogen by the liver, but the liver glycogen is not reconverted to galactose (Harding, Grant, and Glaister, 1934). Furthermore, galactose is but slightly metabolized by tissues other than the liver (Bollman, Mann, and Power, 1935), whilst if there is a renal threshold for galactose it must be exceedingly low (Harding and Grant, 1933). Hence the level of galactose in the blood after administration of a test dose is free from most of the variable factors which confuse the glucose tolerance curve. An oral galactose tolerance test was therefore devised by Althausen, Lockhart, and Soley (1940), and was used both by them and by MacLagan and Rundle (1940) as an additional diagnostic aid in thyrotoxicosis. Whilst these workers agreed that the test was valuable, their opinions differed in regard to the mechanism of the decreased tolerance, for Althausen, Lockhart, and Soley suggested that it was due to abnormally rapid absorption of the sugar from the intestine, but MacLagan and Rundle believed that it was the result of damage to the liver cells which prevented the conversion of galactose to glycogen at the normal rate.

It is generally accepted that the liver may be damaged in severe thyrotoxicosis, for functional tests such as Quick's hippuric acid test and the phenoltetrabromsulphthalein (bromsulphthalein) test often give abnormal results, degenerative or cirrhotic lesions in the liver may be demonstrated histologically, and in extremely severe cases clinical signs of toxic jaundice

¹ Received October 24, 1942.

may be evident. The relevant literature has recently been summarized by Lichtman (1941).

However, there is also evidence that thyroxine influences the rate of absorption of sugar from the alimentary tract, for Althausen and Stockholm (1938) showed that in rats the absorption of glucose and galactose was accelerated by administration of thyroxine, whilst thyroidectomy greatly retarded absorption. In addition, the rate of glucose absorption, which in rats is much reduced after hypophysectomy can be restored to normal by injection of thyroxine (Russell, 1938). Clinical confirmation of this fact has recently come from Althausen (1941), who reported that the diminished galactose absorption observed in patients suffering from sprue could be increased by administration of thyroid substance.

It seemed to us important to determine whether the abnormal galactose tolerance curves found in thyrotoxicosis were due to liver damage or to increased rate of absorption. The high curve is so frequently present in cases which are clinically mild, that to accept it as due to liver damage without further proof might lead to too great emphasis being laid upon thyroid secretion as a liver poison.

If galactose is given to a patient intravenously instead of by mouth it constitutes a metabolic test for liver function which is independent of the rate of absorption (King and Aitken, 1940). A comparison between the oral and intravenous curves in thyrotoxic patients should therefore indicate whether the high oral curve is alimentary or hepatic in origin, for if it be hepatic the intravenous curve must also be abnormal, whilst if it be mainly alimentary the intravenous curve should fall within normal limits. Althausen, Lockhart, and Soley (1940) carried out intravenous curves upon a small series of patients with Graves' disease, and found that their results fell within the range of normal, but they gave no detailed figures for these tests. More recently Bassett, Althausen, and Coltrin (1941) investigated 10 cases of thyrotoxicosis by both the oral galactose test and their modification of the intravenous test. They found the intravenous test significantly altered in only two of the patients.

The object of the present investigation was therefore threefold: (1) to confirm that in thyrotoxic patients there is a diminished tolerance for galactose administered orally, particularly in mild cases of the disease where further diagnostic aids would specially be welcomed; (2) to determine whether the lowering of tolerance is in proportion to the severity of the disease, as judged by clinical evaluation and the basal metabolic rate; (3) to attempt to determine the mechanism by which the lowered tolerance is brought about.

Clinical Material

We have carried out investigations on 40 patients suffering either from thyrotoxicosis of sufficient severity to warrant their admission to hospital for treatment, or from such mild thyrotoxicosis that they were admitted for investigation because the diagnosis was at first uncertain. The cause of the

thyrotoxicosis was a diffuse toxic goitre in 35 patients, and toxic adenoma in the remaining five.

The following factors were taken into consideration in grading the severity of the thyrotoxicosis—rapidity of loss of weight, emotional instability, tremor, cardiac enlargement or arrhythmia, evidence of cardiac failure of thyrotoxic origin, sleeping pulse-rate, and degree of sweating. The patients were graded into four groups on this basis.

Group I (17 cases). This group was composed of mild cases in which the duration of symptoms was usually short. Signs and symptoms were so slight that a long period of rest and medical treatment could be prescribed with confidence before surgical treatment was deemed necessary. Although extremely mild, each patient was diagnosed as suffering from thyrotoxicosis by the physician in charge. The diagnosis was made on the presence of at least two of the features mentioned above, in association with early lid retraction, or demonstrable goitre, or both. The response to treatment confirmed the diagnosis; eight patients eventually underwent subtotal thyroidectomy with complete relief of symptoms, seven others showed unquestionable improvement on Lugol's iodine, whilst the remaining two were relieved with bromide and luminal. The basal metabolic rate, which was estimated in 10 cases ranged from +3 per cent. to +39 per cent., being less than +15 per cent. in five patients.

Group II (16 cases). This consisted of patients with moderate thyrotoxicosis all of whom were in hospital to undergo a course of medical preparation for thyroidectomy. No case was of sufficient severity to occasion undue anxiety during the stay in hospital. In nine cases the basal metabolic rate was estimated and ranged from +20 per cent. to +46 per cent.

Group III (5 cases). In this group were placed extremely severe cases of thyrotoxicosis, all in urgent need of operation after an adequate period of medical preparation. These patients were so toxic that they were a source of anxiety to us, and the one patient in our series who died had been placed in this group before operation; she died in a thyrotoxic crisis after thyroidectomy. The basal metabolic rate was estimated in four of the five patients, and ranged from +58 per cent. to +65 per cent.

Group IV (2 cases). In two patients, one with Graves' disease and the other with a toxic thyroid adenoma, congestive heart failure had occurred some weeks before galactose tolerance tests were performed. Although the patients were well compensated at the time of the tests the liver was enlarged in each case, and for this reason the patients were not included in any of the previous groups. These were the only two patients in our series in whom clinical signs of liver damage were demonstrable.

In addition we have investigated a group of 15 patients who were at one time suspected of mild thyrotoxicosis, but whose subsequent progress showed thyrotoxicosis to be absent. In each case a galactose tolerance test was carried out at the request of the physician in charge as a further aid to diagnosis. In tabulating our results in Table I these patients are listed

under Group V. The final diagnosis was anxiety neurosis in five cases, non-toxic thyroid adenoma in four cases, da Costa's syndrome in two, and hysteria, paroxysmal auricular fibrillation, post-diphtheritic tachycardia, and unexplained loss of weight each in one case.

Finally we have used a control series of 25 normal persons, composed of medical students and house officers; the results of our tests in these cases are set out under Group VI in Table I, and are also shown in Table 3 where they are compared with the control series published by other authors.

Methods

Oral galactose tolerance tests were carried out on the 40 thyrotoxic patients, on the 15 non-thyrotoxic patients in Group V, and on the normal control

TABLE I

Range of Galactose Index and Average Galactose Index in Thyrotoxic Patients, Non-Thyrotoxic Patients, and Normal Subjects

Group	Type of case	Number of cases	Range of G.I.*	Average G.I.*	Number of cases with G.I. under 120
I	Mild thyrotoxicosis	17	16 to 275	137	4
II	Moderate thyrotoxicosis	16	142 to 355	224	None
III	Severe thyrotoxicosis	5	200 to 619	328	None
IV	Thyrotoxic heart failure	2	341 and 639		None
V	Non-thyrotoxic patients	15	2 to 137	63	14
VI	Normal controls	25	10 to 117	54	All

* G.I. = galactose index, the sum of the blood-galactose values in mg. per 100 c.c. at $\frac{1}{2}$, 1, $1\frac{1}{2}$, and 2 hours.

series constituting Group VI. Each patient was starved overnight. In the early part of our investigation a sample of capillary blood was taken from each patient before the tests were started in the morning. This zero specimen, of course, contained no galactose, but it was taken to act as a control on the method of estimation. It was soon found that this check was unnecessary, and thereafter a fasting specimen of blood was not taken. The test was started by the patient's drinking a solution of 40 gm. of galactose in 400 c.c. of cold water; specimens of blood were then taken every half hour for two hours. It is convenient for laboratory technique to have four samples of blood in each tolerance test, and for this reason when a fasting specimen was taken we omitted that at $1\frac{1}{2}$ hours, and *vice versa*.

The galactose in each sample of blood was estimated by the method of Harding, Grant, and Glaister (1933) (see King and Aitken, 1940), in which 0.2 c.c. of blood is used in each estimation. The results were plotted as a graph, and an oral galactose tolerance curve thus obtained. In order that our results might be comparable with those of MacLagan and Rundle (1940) we calculated the 'galactose index' (G.I.) in each case, that is, the sum of the blood galactose values in mg. per 100 c.c. at $\frac{1}{2}$, 1, $1\frac{1}{2}$, and 2 hours. In some of our earlier cases the $1\frac{1}{2}$ hour value was obtained by interpolation, for examination of the curves obtained from the later cases showed that this

did not result in any significant error. In Table I the average G.I. and the range of G.I. is shown for each of our six groups of patients.

Within two days of performing the oral test we carried out an intravenous galactose tolerance test on 22 of our thyrotoxic patients. These consisted of seven mild cases from Group I, 10 moderately severe cases from Group II, three severe cases from Group III, and the two patients recovering from thyrotoxic heart failure in Group IV. An intravenous test was also carried out on 10 of our group of normal students; a larger number of normal subjects was not investigated by the intravenous test, as one of us (King and Aitken, 1940) had already carried out this test on a control series of normal persons and non-thyrotoxic patients. After the patient had fasted overnight a specimen of capillary blood was taken, and then 50 c.c. of 50 per cent. galactose solution injected intravenously, two minutes being taken to complete the injection. Further samples of blood were taken $\frac{1}{2}$, 1, and 2 hours afterwards, the blood-galactose was estimated in each specimen, and the results plotted to give an intravenous galactose tolerance curve.

In order to obtain a single expression for the result in the intravenous test, comparable to the galactose index for the oral test, we have found it convenient to introduce the term 'galactose time' (G.T.). We define this as the time required for the blood-galactose to fall to zero from its value 30 min. after the intravenous injection of 25 gm. of galactose. This is calculated from $\frac{1}{2}$ -hour and 2-hour blood-galactose values as follows. $G.T. = \frac{a}{a-b} \times 90$ where G.T. is the galactose time, 90 the number of minutes between the $\frac{1}{2}$ -hour and 2-hour specimens, a the value for the blood-galactose at $\frac{1}{2}$ hour, and b that at 2 hours.

In Table II are shown the range of galactose time and the average galactose time in our 20 thyrotoxic patients without clinical signs of liver

TABLE II

Range of Galactose Time (G.T.) and Average Galactose Time, in Normal Subjects and in Thyrotoxic Patients

Type of case	Number of cases	Range of G.T.	Average G.T.
King and Aitken's (1940) series*	32	90 to 101	91
Normal controls	10	90 to 104	93
Thyrotoxicosis	20	90 to 106	93
Thyrotoxic heart failure	2	114 and 140	—

* Normal subjects and patients without thyroid or hepatic disease.

damage, in our two thyrotoxic patients with liver damage, in our normal control subjects, and in the 32 patients investigated by King and Aitken (1940) in whom there was neither thyroid nor hepatic disease. Reference to King and Aitken's paper shows that if the galactose time is calculated for their cases of toxic and infective jaundice it is usually found to be definitely, and in some cases greatly, raised above the normal range.

Our patients were admitted to four Sector Hospitals, in only one of which were there facilities for carrying out volumetric estimations of the basal

metabolic rate, and values could be obtained in only 23 of our thyrotoxic patients. The basal metabolic rate estimations were carried out for us by Mr. W. B. Hackett, and we are extremely grateful to him for his co-operation. Estimations were obtained with the Benedict-Roth apparatus in the general ward, as a special metabolic side-ward was not available.

Discussion

Value of the oral galactose tolerance test in diagnosis. One of the points in which we were particularly interested was the value of the test in early thyrotoxicosis, when the differential diagnosis from an anxiety state, da Costa's syndrome, or other causes of persistent tachycardia or loss of weight may be exceedingly difficult.

It was necessary in the first place to determine the normal range of galactose index, for although Maclagan (1940) gave the upper limit of normal as 160, it seemed from our observations that very few normal persons showed an index over 120. For this reason we determined the galactose index of each of our 25 normal controls, and our results are shown in Table III, in

TABLE III
Range of Galactose Index in Non-Thyrotoxic Subjects

Author	Type of case	Number of cases	Range of G.I.	Average	Number of cases with G.I. over 120
Harding and Grant (1933)	Normal laboratory workers	16	9 to 156	52	2
Kosterlitz (1933)	Normal and non-thyrotoxic cases	11	19 to 148	55	1
Maclagan (1940)	Normal and non-thyrotoxic cases	50	3 to 163	68	5
Present series	Normal and non-thyrotoxic cases	25	10 to 117	54	0
Total		102			8

which we have listed also the figures for similar series in the literature. From this it is seen that of 102 non-thyrotoxic subjects only eight showed an index over 120.

Althausen, Lockhart, and Soley (1940) investigated the oral galactose tolerance curve in 10 normal subjects and 87 patients suffering from disorders other than thyrotoxicosis or myxoedema. Detailed figures for each case are not given in their paper, but they showed the average curve for each of these groups, from which it is possible to calculate the average galactose index. For their normal controls the average index was 44, and for their non-thyrotoxic patients 40, values lower than those obtained by other workers, as shown in Table III. Examination of their figures suggests that not more than six of their 97 cases can have had a galactose index over 120. We therefore decided to take a galactose index of 120 as the upper limit of normal for our investigations. It may be noted here that we have on several occasions observed that infections such as mild pulmonary tuberculosis or

rheumatoid arthritis may raise the index above this figure, and in our opinion it is necessary to exclude both active infections and liver disease in a patient before the galactose index can be used as a test for thyrotoxicosis.

It is seen in Table I that in none of our obvious cases of thyrotoxicosis in Groups II, III, and IV was the galactose index within normal limits. Even in our mild cases of thyrotoxicosis in Group I the average index was more than double that of our normal control series, but in four of these 17 cases it was within the upper limit of normal as defined above. At first sight, therefore, it appears that the galactose index is open to the same objection as is the basal metabolic rate, namely that the range of normal is so wide that some early cases of thyrotoxicosis may still fall within it even although the value is raised for the individual in question. This is particularly disappointing, for it is really only in the very early case that laboratory assistance is needed by the clinician.

We have had the opportunity, however, of viewing the test from another angle. We were asked to estimate the galactose index upon a group of 15 patients who were thought by their physicians at the time of the tests possibly to be thyrotoxic. In all these patients this diagnosis was eventually discarded (as described above) and they constitute Group V in Table I, where their average galactose index and range of galactose index are set out. In only one of these patients, suffering from persistent tachycardia after diphtheria, was the index over 120. A comparison between Groups I and V in Table I is striking when it is realized that all the cases in Group V were suspected of thyrotoxicosis at some time, and additional tests were thought necessary to exclude that condition.

We have come to look upon a galactose index over 120 as an additional sign of thyrotoxicosis which is usually present at a very early stage of the disease, but which, like other features, is sometimes absent. The galactose index has therefore to be assessed in company with the clinical findings, and obviously is not in itself an absolute criterion of thyrotoxicosis. The higher the value is above 120 the more likely does thyrotoxicosis become, and above 160 that diagnosis is extremely probable.

Both Althausen, Lockhart, and Soley (1940) and MacLagan and Rundle (1940) have used the test on patients suffering from a wide variety of medical conditions other than thyrotoxicosis. From their experience and our own it seems that the test is unsatisfactory only when there is hepatic disease, Paget's disease, or active infection with fever. MacLagan (1940) and Althausen and Wever (1937) have shown that the presence of diabetes mellitus does not interfere with the interpretation of the oral galactose tolerance test.

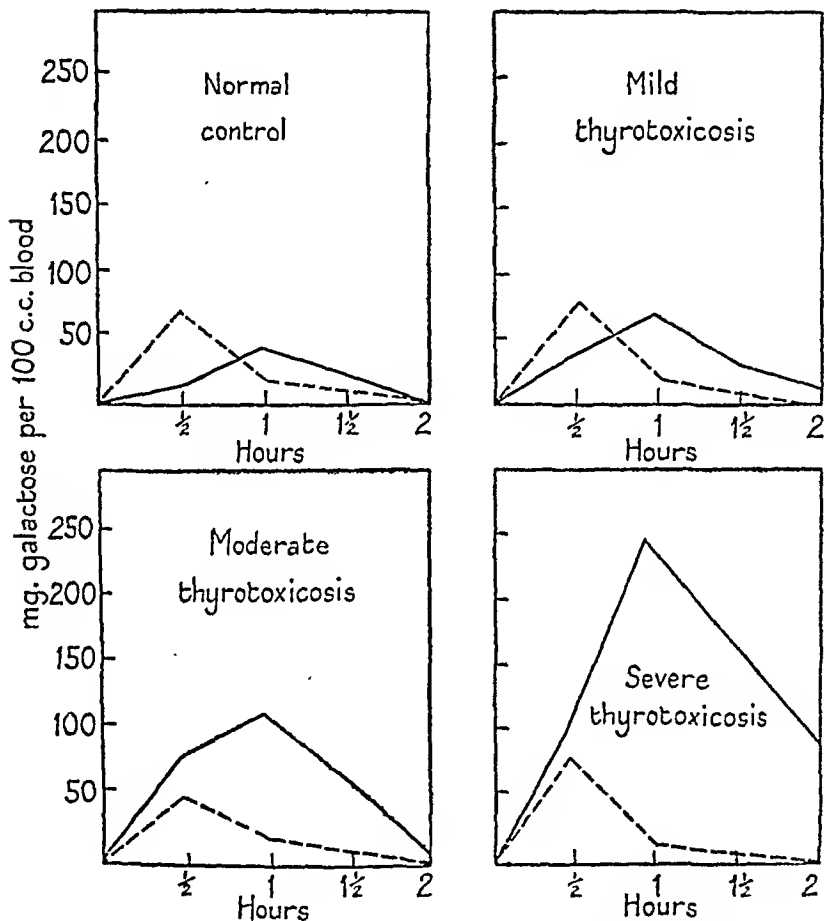
The test has certain advantages over the basal metabolic rate. The technique in the ward is simple, and causes little disturbance or alarm to the patient, for no complicated apparatus is involved. This is a matter of practical importance, for some patients are so emotionally unstable that volumetric estimations of the basal metabolic rate, even when repeated

on several occasions, are extremely unreliable. Maelagan and Rundle (1940) have shown that, unlike the basal metabolic rate, the galactose index is relatively little affected by iodine therapy, and rightly stress the importance of this, since so many patients now attend hospital for the first time having already undergone treatment with iodine. Other advantages of the test are that the specimens of blood can be taken by a laboratory technician, and no apparatus or reagents are required other than those which can be found in any hospital laboratory. It can therefore be used as an accessory test when a metabolic side-ward and the more expensive and cumbersome apparatus for the basal metabolic rate are not available. In addition the laboratory technique is but little more complicated than that for blood-sugar estimations by the usual titrimetric methods. Finally, we believe that it is a more satisfactory test than the metabolic rate for out-patients, who require a long rest after their arrival at hospital before volumetric estimation can be undertaken.

Relationship between the galactose index and the severity of the thyrotoxicosis. We have attempted in our patients to correlate the level of the galactose index in turn with the basal metabolic rate and with each of the clinical features upon which we have assessed the severity of the cases. In our series there is no close relationship between the basal metabolic rate and the galactose index. In view of the fact that Althausen and Stockholm (1938) were able to raise the basal metabolic rate of rats to +100 per cent. by means of α -dinitrophenol, without thereby affecting the rate of absorption of galactose, we should not have expected any close correlation. Furthermore, Althausen, Lockhart, and Soley (1940) could detect no close quantitative relationship between the basal metabolic rate and the galactose tolerance test in their thyrotoxic patients. Maelagan and Rundle (1940) were of the opinion that there was a clear general relationship between the clinical grade of thyrotoxicosis, basal metabolic rate, and the galactose index, but after a study of their paper we cannot consider their evidence conclusive. It is possible that some of the discrepancy between galactose index and basal metabolic rate in our cases is to be explained by the fact that a number of our patients had received iodine before admission to hospital, and iodine therapy is known to affect the basal metabolic rate more than it does the galactose index. Similarly, attempts to correlate the galactose index with any one of the clinical features of these patients has been unsuccessful, and yet the index does appear to be proportional to the clinical assessment as a whole, which in turn is based upon a combination of all these features.

Mechanism of the galactose tolerance test. Table I shows that the galactose index was raised above the normal average in all our groups of thyrotoxicosis, but Table III shows that the galactose time was always within normal limits, except in the two patients with liver damage from heart failure. This point is brought out in the Figure, in which the intravenous and oral galactose tolerance curves are plotted for a normal subject and for a typical example from each of our groups of thyrotoxicosis.

It is conceivable, although unlikely, that increased utilization of galactose by the tissues might occur in thyrotoxicosis, and so allow the intravenous test to give normal results even in the presence of liver damage. For this reason we estimated in five patients the arteriovenous galactose difference during the intravenous test, and found that the difference was negligible,



Comparison between oral and intravenous galactose tolerance curves in a normal control, and in typical cases of mild, moderate, and severe thyrotoxicosis.

Continuous line, 40 gm. of galactose by mouth. Broken line, 50 c.c. of 50 per cent. galactose solution intravenously.

being between 5 and 7 mg. per 100 c.c. Harding and Grant (1933) found similar arteriovenous differences for normal subjects, and MacLagan (personal communication) has carried out similar tests upon thyrotoxic patients with the same result.

Another possible explanation of the high galactose index in thyrotoxicosis is that less galactose might be excreted in the urine in this disease than is excreted by normal subjects, but Lichtman (1932) estimated the urinary output of galactose in 13 thyrotoxic patients after oral administration of

a test dose, and showed that it was normal in seven cases and greater than normal in the remaining six.

It seems certain, therefore, that the high oral galactose tolerance test in thyrotoxicosis is the result of increased rate of absorption rather than liver damage. We wish to emphasize that we do not doubt that hepatic damage does occur in severe thyrotoxicosis, and can be demonstrated by tests more delicate than the intravenous galactose tolerance test. Our point is that a galactose index above the normal range occurs in many patients with the mildest degree of thyrotoxicosis, and that the mechanism of this particular test lies in the rapid absorption of the sugar and not in liver damage.

If our contention be correct, it might be expected that the peak of the oral galactose curve would occur at an earlier time in thyrotoxic patients than in normal subjects. Our results do not furnish any evidence on this point, since no specimens of blood were taken earlier than 30 min. after ingestion of the sugar. In none of our cases, however, was the peak of absorption in the thyrotoxic patients at a later time than in the normal controls. Althausen, Lockhart, and Soley (1940) took blood samples at 5 and 15 min. after ingestion of galactose, and found that the sugar appeared more quickly in the blood and rose more rapidly in their thyrotoxic patients than in their normal controls.

Althausen and Stockholm (1938) have shown that the rate of absorption of galactose is dependent upon the speed of phosphorylation in the intestinal mucosa. It seemed possible that this increased rate of absorption in thyrotoxic patients might show itself by a fall in the plasma inorganic phosphate during absorption. We therefore estimated the plasma inorganic phosphate in each specimen of blood taken during the oral galactose test in three patients with severe Graves' disease. No constant significant change was found and we cannot therefore throw any further light upon the mechanism by which the increased absorption is brought about in these patients.

Summary

1. Oral galactose tolerance tests have been carried out on 40 patients suffering from thyrotoxicosis, and intravenous galactose tolerance tests upon 22 of these cases.

2. The value of the oral test in the diagnosis of early thyrotoxicosis is discussed.

3. The finding of normal intravenous galactose tests with abnormal oral tests suggests that the latter are the result of abnormally rapid absorption of the sugar from the intestine.

We wish to thank the Emergency Medical Service physicians in Sector VI and the Staff of the Middlesex County Council Hospitals in that Sector who have allowed us to carry out investigations on their patients. We are also indebted to Dr. K. W. Cross who gave us much valuable help in the early part of our work during his tenure of office as House Physician at one of the Sector Hospitals.

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INFECTIVE HEPATITIS¹

By J. D. S. CAMERON

With Plates 15 and 16

Introduction

THE work reported in this paper was carried out at two Army General Hospitals in Palestine during 1940 and 1941, when infective hepatitis appeared in epidemic form among the troops. The disease had already begun to be noticed in 1938, when Major W. H. Hargreaves drew attention to cases in a mounted unit, and suggested that association with the horse might play some part in the aetiology. The suggestion that the present work should be undertaken came from the D.D.M.S., British Forces in Palestine, and the Consultant Physician, Middle East Force, and we were provided with full facilities and abundant co-operation, both military and civil.

The concept of epidemic hepatitis. There can be little doubt that modification must be made in the original concept of catarrhal jaundice advanced by Bamberger (1855), supported by Virchow (1865), and upheld by most physicians until recent years. It was generally maintained that the initial lesion was a gastroduodenitis followed by spread of 'catarrh' to the epithelium of the bile-ducts, thereby producing an obstructive jaundice. The same view was accepted by pathologists, and the usually benign prognosis has delayed the elucidation of the true pathology. The occurrence of a biphasic van den Bergh reaction raised doubts about the simple explanation, and suggested that liver damage must be combined with biliary obstruction, if, indeed, the latter was present at all. Many physicians have claimed that two conditions exist—true catarrhal jaundice with the obstructive element predominating and little, if any, hepatic involvement, and infective hepatitis in which liver damage is of major and biliary obstruction of minor importance. The cases discussed in the present report undoubtedly fall into the second category and the term infective hepatitis has been used in preference to catarrhal jaundice. Further, we are of opinion that in some instances hepatitis is present without jaundice occurring at all, although the other clinical symptoms and signs characteristic of the disease are evident.

Recent descriptions of infective hepatitis. The disease appears to occur throughout the world, independently of climate, generally with the greatest incidence in autumn. In Britain many outbreaks have been reported in recent years, all of which bear a striking similarity to the epidemic now

¹ Received October 21, 1942.

reported. Sergeant (1937) described an outbreak among schoolchildren at Gateshead-on-Tyne, while Lisney (1937) reported a similar occurrence in schools of Lincolnshire. Barber (1937) gave an account of two institutional outbreaks and concluded that 'most catarrhal jaundice is infective hepatic jaundice'. Maitland and Winner (1939) reported a small outbreak in a ward of a London hospital. Cullinan (1939) has given a complete summary of epidemics in England since 1926. He regards the disease as resulting from droplet infection and developing, after an incubation period of 21 to 35 days, through premonitory symptoms to jaundice. He still considers that there are two types, catarrhal and infective jaundice. The papers of Findlay, MacCallum, and Murgatroyd (1938), and Findlay (1940) bear especially on problems of aetiology, but provide a good review of the whole literature up to these dates. Recent reports from other countries include den Hartog (Holland, 1937), Deines (Germany, 1938), Bloch (Switzerland, 1939), and Norton (United States of America, 1939). Fauque (1937) discussing jaundice in the French Army recognized spirochaetal catarrhal and simple infective forms. His clinical description of the latter is similar to our own, but there is a wide discrepancy in his estimation of the duration of the incubation period. Papers by Andersen (1937, 1938) and Andersen and Tulinius (1938) from Denmark are referred to in the discussion on aetiology.

Infective hepatitis in Palestine. Civilian. There are only a few published records, all of recent date, but discussions with civilian physicians in Jerusalem and Haifa show that the disease has been prevalent and widely recognized in Palestine and adjacent countries for many years. A valuable unpublished report to the Government Health Department by Dr. S. Btesh of Haifa fully supports this view. It appears that the disease has been regarded as sporadic rather than epidemic, that young people and especially children are prone to infection, and that new arrivals in the country are more likely to be infected than those born in Palestine. Spirochaetal jaundice has also been encountered, but all were agreed that the sporadic cases were not of this type. The view was advanced by many physicians that a large number of children acquire the disease in a mild form and are immune for life, thus reducing the incidence in the adult native population. With each new immigration of settlers a new non-immune child population is added, and this accounts for epidemics in children during their first two years in the country. So well known is this belief that the disease has been called 'German jaundice', since so many immigrants have come from that country. The arrival of British troops represents another immigration, the only difference being in age. The recent published reports in Palestine are by Yenikomshian and Dennis (1938) of an outbreak in Lebanon with five deaths, and by Jossem (1940) who met with 51 cases in the Agricultural School of Mikveh Israel between January 1938 and February 1940. Valuable unpublished observations from other hospitals have also been generously placed at our disposal and fully discussed prior to the writing of the present report.

Military. The presence of the disease was first commented on by Major Hargreaves in 1938. During 1939 cases continued to appear, but it was not until 1940 that epidemic figures were reached and 342 cases were notified. The incidence in 1940 and 1941 is given, month by month, in Table I, but it must be noted that the number of troops in the country during these two years varied greatly.

TABLE I

Monthly Record of Cases during 1940 and 1941

A = Cases observed in a General Hospital

B = Total military cases notified in Palestine, including A

1940	January	February	March	April	May	June	July
A	3	5	6	1	3	5	9
B	7	15	10	3	4	11	21
	August	September	October	November	December	Total	
A	9	11	60	44	46	202	
B	18	23	87	66	77	342	
1941	January	February	March	April	Total		
A	29	7	6	6	48		
B	79	19	17	11	126		

I. CLINICAL PICTURE

(In collaboration with Captain D. G. COLVILLE, R.A.M.C.)

In all, 250 cases have been studied and the following account is based on the clinical records of 170 patients.

Pre-icteric stage. After a long incubation period (shown later to be 32 days as a minimum) the disease starts in a way closely resembling Sand-fly fever, and in fact this was the initial diagnosis in the majority of the early patients in the epidemic. Fever, malaise, and headache are present in both conditions at the outset, but in infective hepatitis the headache is less intense. Moreover, it lacks the characteristic pain in, behind, and on movement of, the eyes found in Sand-fly fever. Anorexia is invariable and far greater than in Sand-fly fever; in fact the importance of the initial anorexia cannot be over-emphasized and is so complete that all food may be refused for two or more days. Disinclination for smoking is also present. Nausea is common, but vomiting unusual. The tongue is clean, but a taste variously described as 'like rubber', 'sour', or 'bitter' is often complained of. Labial herpes was never noticed, a point of difference from spirochaetal jaundice. Abdominal discomfort, more a tightness than a pain, was common in the right upper abdomen, and the bowels more often showed a tendency to constipation than diarrhoea. Fever was present in all cases observed during the pre-icteric stage. It was of fairly regular type, varying as a rule between 99° F. and 103° F. (highest 104° F.) and continued for three to six days (see Figs. 1 and 2) when jaundice appeared. In a number of cases when the fever abated the patient still remained unwell, and three to 10 days later another bout of fever ushered in jaundice. Dr. Btsh of Haifa considers that jaundice

more often occurs with the second period of fever than the first, and so has divided the clinical picture into four stages of (1) initial fever, (2) intermediate period, (3) hepatotoxic stage with fever, and (4) jaundice. A few cases showed continued fever up to 14 days which did not terminate when jaundice developed. Others showed the initial pyrexia followed by a low fever lasting up to 14 days after jaundice appeared.

Jaundice. There is a clinical opinion in Palestine that the disease may occur without jaundice at all, but the present description refers to our cases in all of which jaundice was present. The prodromal symptoms, already described, continued for one to eight days prior to the discovery of icterus, the average duration of the pre-icteric stage in 170 patients being five days. With the development of jaundice the initial symptoms rapidly subsided, and in many cases appetite returned within four days. Anorexia continued, however, with diminished intensity in cases in which bile remained absent from the stools for longer than usual. Fever ceased as a rule whenever jaundice appeared. The depth of jaundice varied greatly, from a light coloration of the conjunctivae to a deep icterus involving the whole body, and appeared to bear a relationship to the severity of the symptoms. The average duration in 170 cases was 21 days (maximum intensity at five days), but it ranged from five to 72 days. Itching was complained of by only eight patients on admission, but others developed this symptom later. Severe cholaemic symptoms were present in one officer who was very deeply jaundiced, and to a lesser degree in six other patients. Disturbance of visual accommodation was twice reported. Bradycardia occurred as soon as jaundice developed, but this seems to accompany all virus infections and is very noticeable after Sand-fly fever. It may be noted that during the pre-icteric stage tachycardia is the rule.

Other symptoms and signs. Enlargement of the liver was noted in 97 of the 170 patients, the average being to $1\frac{1}{2}$ fingers' breadth below the costal margin, and the largest three fingers' breadth. The enlargement was transient, lasting seven to 14 days in most cases. In the greatest enlargement of all return to normal was noted after 12 days. Tenderness in the hepatic area was present in 109 cases, associated with liver enlargement in 89 and without enlargement in 20 cases. A palpable gall-bladder was detected twice. Splenic enlargement was noted in 46 cases, usually to two fingers' breadth below the ribs, and the organ felt firm on palpation. Hepatic enlargement was found in only 34 of these cases. Our figures, it should be stated, are not in full accord with those of other observers in Palestine, who describe enlargement of both organs in by far the majority of patients. Jossem (1940) has stated that 'splenic enlargement varies in degree and is in no relation to the severity of the disease'. In 'the light cases the enlargement is often conspicuous, whereas in severe cases it is even difficult to demonstrate'. The difference in our figures may be partly explained on age incidence, since the vast majority of civilian patients in Palestine are children. Nervous and ocular signs may be expected in a disease strongly

suspected as due to a virus. In two patients mental disturbance occurred; in one jaundice was intense and the mental state was attributed to hepatic insufficiency, but in the other the mental disturbance was more severe

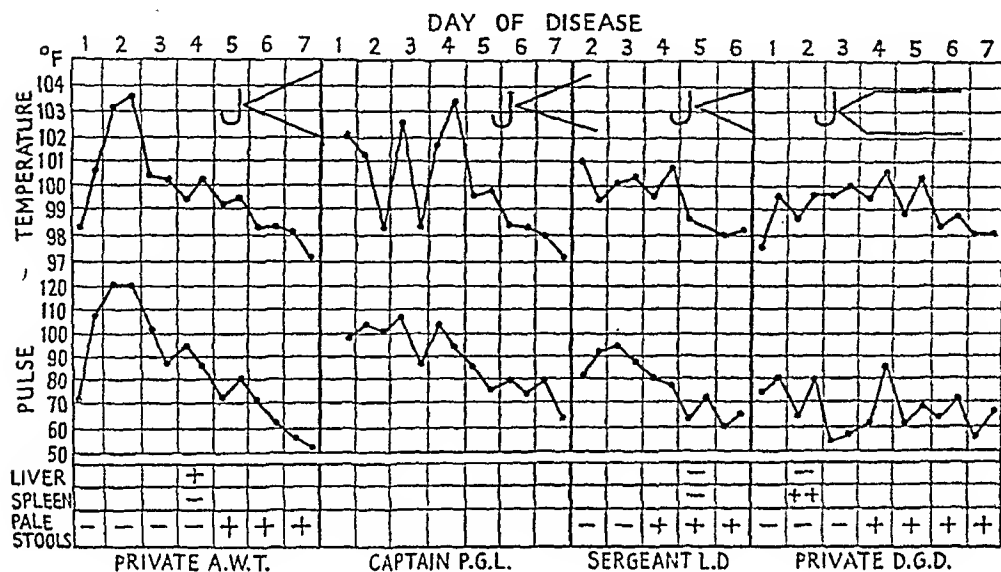


FIG. 1

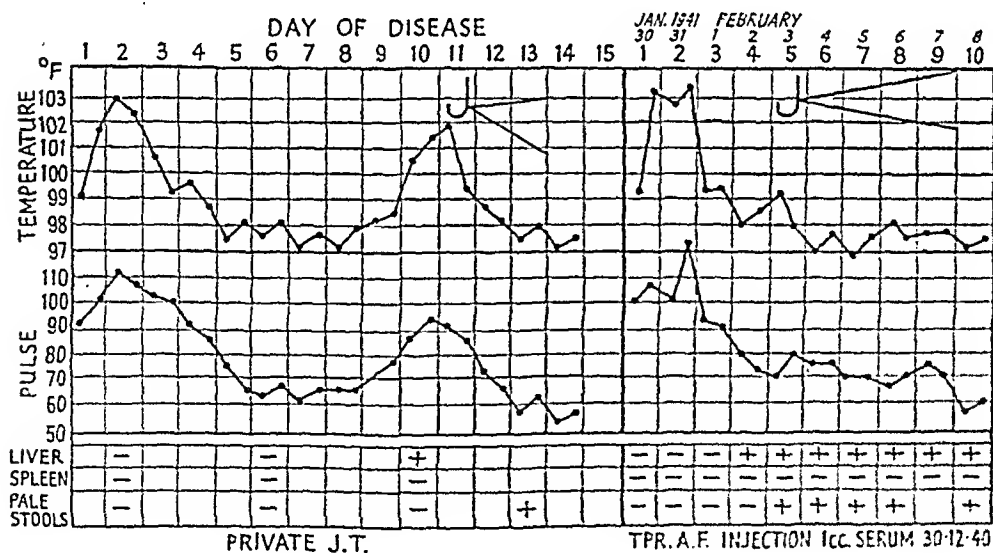


FIG. 2

although jaundice was slight. In three patients temporary ocular difficulty with accommodation was reported, but iridocyclitis (comparatively common in Sand-fly fever) was never found. Meningitis, which also occurs in virus infections, was never seen by us, and two cases reported from another hospital were probably cerebrospinal meningitis in which intercurrent infective hepatitis developed.

Urine examination. Bile was present in all cases, generally appearing on the day prior to the clinical recognition of jaundice. The average duration was nine days, excluding three patients with very prolonged jaundice. Urobilinuria may be noted in the pre-icteric stage and again when biliruria has ceased. During the febrile stage albuminuria is frequent, but never for longer than four days, and tube-casts and blood-cells were never found. The urinary sediment from 40 cases was injected intraperitoneally into mice to exclude leptospiral infection. All results were negative.

Faeces examination. In most jaundiced patients the first stool passed after admission was light-coloured, but in some was normal. The stools became clay-coloured in about half of the patients, but in 12 were reported as normal throughout the illness. The average duration of light-coloured stools was eight days, excluding three prolonged cases. Fat analysis of a typical stool at the light stage gave the following result: Total fat in dried stool 46.7 per cent., free fatty acids 30 per cent., combined fatty acids 16.7 per cent. Bacteriological examinations, both during the light- and normal-coloured stages, were all negative. Many cases of jaundice in Gallipoli during the last war were associated with Paratyphoid B infection, but this organism was not found, nor did agglutination tests in 40 consecutive cases support this hypothesis.

Blood examination. Leucocytosis was never found; on the contrary, leucopenia was present in many cases, but not in all. Differential counts showed an invariable neutropenia. The average of a number of blood counts was as follows:

Total white-cell count	.	.	6340 (8400 and 3700) per c.mm.
Neutrophil polymorphs	.	.	47 % (65 % and 28 %)
Eosinophil polymorphs	.	.	2 %
Basophil polymorphs	.	.	1 %
Lymphocytes	.	.	43 % (60 % and 26 %)
Monocytes	.	.	7 % (13 % and 1 %)

(The figures in brackets represent the highest and lowest in the series.)

The absence of leucocytosis at any stage was regarded as additional evidence against spirochaetosis ictero-haemorrhagica.

Other tests. Many additional clinico-pathological tests were carried out, including tests for liver efficiency, blood coagulation time, bleeding time, and blood sedimentation rate; all were within normal limits.

Histamine test. This test, introduced by Klein (1931) for the diagnosis of latent jaundice, proved a valuable help in the diagnosis of the pre-icteric stage of infective hepatitis, and was often positive two to three days before visible icterus was noticed. The test consists in the intradermal injection of 0.25 c.c. of a suitable histamine preparation into a clear area of skin, the inner aspect of the forearm being generally chosen. In the normal subject a characteristic wheal ensues with a white centre. In the pre-icteric stage of hepatitis the hyperaemic edge of the wheal is yellow within $\frac{1}{2}$ to 1 minute, and the whole of the wheal is soon uniformly yellow.

Incubation period, period of infectivity, and contact infection. All patients

were asked to give a list of close contacts in their unit, and this was compared with all other lists and the names of previous sufferers from the disease. In a remarkably large number of instances contact was readily established, and moreover chains of cases of infection in various units were quickly recognized. From this evidence a tentative minimum incubation period of 32 days was arrived at. It was soon evident that a much longer incubation period must be allowed for in many cases, if the contact assumed to be the source was correct. The hypothesis was made that in such delayed cases the liver was resistant at the time of infection, but later became suitable soil because of some accessory factor such as alcohol, other illness, chill, low diet, or fatigue. The occurrence of hepatitis in the course of some other disease was frequent, wounds, appendicitis, malaria, cerebrospinal fever, diphtheria, and scarlet fever all providing examples. There was also a heavy incidence of the disease following periods of active service in the field. Two interesting examples of contact infection are worth description in full. A private shooting camp was maintained in one area of Palestine, and between September 30 and October 6 this was used by four officers from different units who had not previously met. They were accompanied by three servants and an Arab interpreter. All dispersed to their units on October 6. One officer was admitted to hospital with infective hepatitis on November 2, one servant on November 5, and the three remaining officers on November 6. A second servant became jaundiced during December, and as far as is known the remaining servant escaped infection. The Arab interpreter could not be traced. In this series the incubation period appears to vary between 28 and 38 days, except for the servant who fell ill two months after contact.

The second series, illustrating the chain spread of infection, occurred in the staff of the hospital in which our work on infective hepatitis was done.

TABLE II

No.	Name	Onset	Suggested association or contact
1	Capt. C	13/8/40	Both patients in the officers' ward of Hospital A suffering from infective hepatitis
2	Lieut. B	14/9/40	
3	Corpl. H	1/10/40	Nursing orderly attending 1 and 2
4	Private D	29/9/40	Office staff, slept next to No. 3
5	Private Y	29/9/40	Dental staff, slept in same small room as Nos. 3 and 4
6	Private B	14/10/40	Dental staff, in close association with No. 5
7	Sergt. D	16/10/40	Cook, no close association with any of above
8	Private K	20/10/40	In office of Hospital A with No. 4
9	Private C	23/10/40	In office with, and close friend of, No. 4
10	Sister C	28/10/40	Night sister in hepatitis ward
11	Private S	30/10/40	Day orderly in hepatitis ward
12	Private G	6/11/40	Laboratory staff, close friend of Nos. 4 and 9
13	Private S	18/11/40	Day orderly in hepatitis ward
14	Private A	17/1/41	Close associate of, and slept next to, No. 8. in Hospital B

In Table II the entire incidence of hepatitis in the hospital staffs is set down. It will be noted that all but one had direct and close contact with a source of infection and that spread from one hospital to another apparently ensued. The occurrence of the disease in a nursing sister and two orderlies

engaged in the care of cases of hepatitis is of significance in showing the contagious nature of the disease and the need for isolation of patients. The period of infectivity is obviously important, and although no positive statement can be made, the study of hospital incidence strongly suggests that infection may spread during part of the incubation, the pre-icteric, and a portion at least of the icteric stages. Metsch, in Palestine, states that 'the patients continue to be infective for a long period, even after all traces of jaundice have disappeared'.

Diagnosis. The diagnosis presented no difficulties in the epidemic circumstances in which our study was made. Five points were recognized to be of major importance in the diagnosis during the pre-icteric stage, and allowed early isolation: 1, anorexia, 2, abdominal discomfort, with or without hepatic enlargement and tenderness, 3, absence of leucocytosis, 4, increased urobilinogen in the urine, and 5, the histamine wheal test for latent jaundice. In differential diagnosis the chief difficulties were Sand-fly fever, during the early pre-icteric stage, and malaria. In the latter disease it should be noted that infective hepatitis has been observed as an intercurrent infection. The diagnosis from spirochaetosis ictero-haemorrhagica presented no difficulty, in the absence of leucocytosis and renal signs, although the positive tests (excepting inoculation of mice with urinary sediment) were not available to us. Obstructive jaundice, with its many causes, was excluded by clinical observations.

Prognosis. No deaths occurred in the full clinical series observed by us, and in most of the patients recovery was complete in 35 days. A few continued beyond six weeks, and in three patients the duration was over 70 days. Relapse occurred in two patients about a month after discharge from hospital, and no genuine second attacks were met with. The latter point is in accord with the opinion held by civil doctors in Palestine that one attack confers immunity.

Treatment. Isolation of the patient must be insisted on as far as possible because of the evidence of infectivity, and on our view that lowered resistance of the liver predisposes to infection there should be no mixing with other acutely ill patients. The essence of treatment lies in recognition of the fact that this is a liver disease and not a skin coloration, and a minimum of one month in hospital was found necessary in the mild cases, even although jaundice had disappeared much earlier. No patients were allowed out of bed for at least a fortnight, and disappearance of pyrexia, return of appetite, and fading of icterus, although valuable indications, must not be taken as evidence of complete recovery of hepatic function. The patient's appetite was taken as the guide and a diet containing high carbohydrate, liberal protein, and normal fat was reached as early as possible. The presence of clay-coloured stools was held to be the only justification for a diet low in fat and cholesterol, and where the stools remained persistently pale, bile salts were given so that fat could be introduced with the diet. Haemorrhage did not occur in any patients of our series, but in view of the

haemorrhagic lesions found in fatal cases we made use of all possible natural sources of vitamin K, since no special preparations were available. In a later case, seen in India, epistaxis occurred every time the patient sat up for any length of time, but this ceased immediately after the intravenous injection of vitamin K. All patients were instructed to abstain from alcohol for a minimum period of three months, on the view that alcohol lowered the resistance of the liver and that the hepatitis might be incompletely healed.

II. EXPERIMENTAL

(In association with Professor I. J. KLIGLER, Department of Hygiene, Hebrew University, Jerusalem, and Captain D. G. COLVILLE, R.A.M.C.)

Historical. Andersen (1937, 1938) and Andersen and Tulinius (1938) reported the successful transmission of epidemic hepatitis in pigs, from man to pig, and from rat to pig. They considered that for successful transmission a lowered vitality of the recipient was necessary. Apart from these experiments no reference to successful transmissions in animals has been found in the available literature. Findlay (1940) and Findlay, MacCallum, and Murgatroyd (1938), following the occurrence of hepatitis in men who had been immunized against yellow fever, attempted to transmit the hepatic disease to monkeys, hedgehogs, cats, dogs, ferrets, rabbits, guinea-pigs, rats, field voles, fowls, mice, and pigeons. Pathological material was introduced by subcutaneous, intraperitoneal, and intravenous injections, by intranasal instillation and by feeding. All the experiments were negative, as were also injections into developing chick-embryos. Findlay and his co-workers considered that the hepatitis following immunization for yellow fever must be due to the human serum in which the immunizing substance was made, and one donor of blood was known to be a previous sufferer from hepatitis. Later preparations of sera, obtained from selected donors with no previous history of jaundice, were never associated with hepatitis. They concluded that the evidence pointed to an extraneous agent capable of propagation in blood-serum, this agent being almost certainly a virus. Their experiments link up with the report of Probert (1938) who described the occurrence of hepatitis in seven children injected with convalescent measles serum. Three of these children died of acute necrosis of the liver, and two contacts, who had not received any serum, developed hepatitis with jaundice two months later. Hepatitis has also been noted in horses after immunization with horse-serum preparations against horse sickness (Theiler, 1919), equine encephalomyelitis (Marsh, 1937), and grass sickness (Gordon, personal communication, 1938). Slagsvold (1938) reported 50 deaths in horses with evidence of acute or subacute liver necrosis after anti-anthrax injections in a medium of horse serum. No such accidents followed injections when cows' serum was used. In reporting the early human cases of hepatitis in the Army in Palestine in 1938 and early 1939, Major W. H. Hargreaves, R.A.M.C., noted that they occurred predominantly in a cavalry unit and

that jaundice was also prevalent at the same period in horses. The horse jaundice, however, was proved to be due to biliary fever or piroplasmosis, the equine variety of which is caused by either *Babesia caballi* or *Nuttallia equi*. Both of these piroplasms are tick-borne, the vectors for the former being *Dermacentor reticularis* and for the latter *Rhipicephalus bursa* or *evertai*. These piroplasms invade the red blood-cells and cause haemolytic jaundice, associated with collapse, cardiac failure with oedema, and occasionally haemoglobinuria (Wooldridge, 1934). No associated hepatitis has been reported in the literature.

General Laboratory Experiments (in collaboration with Professor I. J. Kligler, Hebrew University, Jerusalem)

Samples of blood were withdrawn from patients as soon as possible after a diagnosis of hepatitis had been made, and included some from the pre-icteric pyrexial stage, the icteric-pyrexial stage, and the later icteric non-pyrexial stage. Part of the blood was allowed to clot, but sodium citrate was added to the larger portion to prevent clotting. Samples were taken to the laboratory in thermos flasks over ice. Some animals received whole blood or plasma without further treatment. In others a leucocytic fraction was prepared by centrifugalizing the citrated blood for an hour, the resulting sediment being then suspended in saline and injected. Only young laboratory animals were employed, a number of them being previously starved.

TABLE III

Animal	No. used	Method of injection
Monkey	1	Whole blood intraneutaneously and subcutaneously
Guinea-pigs	6	3 received whole blood in the heart
		3 received leucocytic sediment in the liver
Dogs	4	Whole blood in heart and liver
Mice	30	10 received leucocytic sediment intranasally and in the liver
		10 leucocytic sediment intracerebrally
		10 whole blood intraperitoneally
Rats	18	6 leucocytic sediment intranasally and in liver
		6 leucocytic sediment intracerebrally
		6 whole blood intraperitoneally
Hamsters	8	4 leucocytic sediment intranasally and into liver
		4 whole blood intraperitoneally

Two to four 'passages' were made from all the animals, except the monkey, the same routes being employed, while passage was also attempted from guinea-pigs to mice and from dogs to guinea-pigs. Injections were also made into chick embryos at the fifth day of development (four experiments) and thirteenth day (five experiments). From later cases of human hepatitis nasal washings were also taken in normal saline and injected as follows:

- (a) unfiltered, intraperitoneally and intranasally into mice;
- (b) filtered, intraperitoneally and intranasally into mice;
- (c) filtered, intracardially into guinea pigs.

Passages from these animals were made as before. Careful clinical observations, blood counts, and temperature charts (of the monkey, guinea-pigs,

and dogs) were made, but all the experiments must be reported as completely negative. In the guinea-pigs, however, some suspicious findings of interest may be reported. In all of them a leucopenia appeared 5 to 20 days after injection, and one animal showed necrosis of liver cells and round celled infiltration of the portal tract. In a control series injected with normal blood and normal liver the same blood changes were found, but no liver lesion.

Horse Experiments (with Captain D. G. Colville, R.A.M.C., and Captain Hynds, R.A.V.C.)

The occurrence of jaundice in horses, already referred to, raised the necessity of excluding piroplasmosis as a cause of the human hepatitis. Human patients were questioned about infestation with ticks, but no evidence was found. In spite of this and the clinical differences between the haemolytic icterus in piroplasmosis of horses and the human disease, under discussion, it was thought desirable to carry out experiments in horses. Injection experiments from human cases of hepatitis were carried out in six horses. These animals were first examined and reported on by Captain Hynds, R.A.V.C., and a complete blood count was done. Thereafter 2 c.c. of whole blood or serum from human cases were injected intramuscularly into the hind quarters. Blood counts were repeated at intervals and the animals kept under close veterinary observation. All the experiments were negative.

Human Experiments (with Captain D. G. Colville, R.A.M.C.)

A call was made for volunteers to be inoculated with blood from jaundiced patients, and an immediate response was obtained from one cavalry regiment and later from another which, however, was prevented from participating by service conditions. Seven volunteers from the first unit were used. Careful clinical examination, investigation for possible contact, and complete blood examination preceded the experiments in which 1 or 2 c.c. of 'infected' whole blood or serum were injected intramuscularly into the buttock. The volunteers were kept under constant supervision by the Regimental Medical Officer and reported to us weekly for examination and blood count, until active service prevented their attendance. It was intended to continue the experiments with filtered serum, nasal washings, and salivary washings in an attempt to establish a virus infection and in the hope of discovering its mode of dissemination, but while these initial observations were in progress deaths from human hepatitis began to occur, and a study of the human pathology (described in Part III) deterred us from continuing the human experiments. Of the seven volunteers inoculated, one was transferred to a special field duty at a distance, and was lost sight of. Of the remaining six, one developed jaundice one month after injection, a second within two months, and the remaining four within six months. The details of the first case are given in full:

Volunteer I

- 30/12/40. Received 1 c.c. of unfiltered blood-serum intramuscularly, the serum being obtained from an apyrexial case of infective hepatitis on the second day after jaundice developed.
- 29/1/41. In the evening anorexia, headache, and mental depression.
- 30/1/41. Above symptoms increased, with fever and pain in the back.
- 3/2/41. Symptoms unabated. Jaundice appeared.
- 4/2/41. Jaundice increased. Pyrexia ended. Felt better, but marked anorexia, stools pale.
- 18/2/41. Jaundice disappeared clinically, but icterus index was still 20.

The liver was enlarged 1 inch below the costal margin from 1/2/41 to 13/2/41, but the spleen was never palpable. After discharge from hospital, this volunteer returned to full duty with his unit, and remained well. He died of wounds received in action in June 1941.

During this volunteer's illness a number of investigations were made (see Table IV).

TABLE IV
Differential Count of Leucocytes

Date	Total per c.mm.	Poly- morphs %	Eosino- phils %	Baso- phils %	Mono- nuclears %	Lympho- cytes %
30.12.40	10,600	58	3	0	6	33
8.1.41	8,400	63	3	0	4	30
17.1.41	8,600	65	4	0	5	26
26.1.41	6,200	58	3	0	6	33
31.1.41	5,600	46	6	0	6	42
2.2.41	6,800	42	8	0	4	46
3.2.41	7,200	47	4	0	6	43
8.2.41	6,000	54	4	0	8	34
12.2.41	7,800	51	4	0	6	39
18.2.41	7,400	58	3	0	4	35
25.2.41	8,200	64	2	0	5	29
3.3.41	8,600	66	2	0	4	28

In the Table, counts above the line were made prior to the onset of illness, and those below the line during the disease. Icterus index was 70 on 4/2/41, 40 on 10/2/41, 20 on 17/2/41. Serum Phosphatase (Bodansky) 19.5 units at beginning, 3 units at end of illness. Cholesterol 126 mg. per 100 c.c. at beginning, 150 mg. per 100 c.c. at end of illness.

Blood and nasal washings were taken from volunteer I, and injected into volunteer II. Up to six weeks after injection no illness followed, when the man left on active field service. Of the five other volunteers injected with 1 c.c. of blood serum or 2 c.c. of whole blood from infective hepatitis in the pyrexial stage, all were observed for periods up to six weeks, but they then proceeded on field operations. During the next six months, while under active service conditions, all developed jaundice. No full observations could be made, but the histories of their illnesses seemed typical of infective hepatitis. The first fell ill after one month on field service, the last just under six months after injection. This last case was severe, being icteric from 30/8/41 to 14/9/41. He was seen by us some time later, and gave the following account of himself: 'A month after the injection I felt out of sorts and passed dark urine. I saw the regimental medical officer, but there was

no need for hospital. I stuck it out well during the hard marches of the campaign, but just when it was over I went and got the jaundice.' During their period in the field a number of other cases of infective hepatitis occurred in the same unit, but the incidence was low, specially compared with 100 per cent. as in the six volunteers. In commenting on these results, we fully realize that the experiment is not a perfect one. While, therefore, it cannot be stated with certainty, it seems probable that the six volunteers who were traced suffered from jaundice as a result of the inoculations, and that in five of them the onset was delayed until the hard conditions of field service rendered them susceptible to the disease. We must also admit the unfortunate fact that these five men may have been the innocent cause of other cases in men exposed to chill, fatigue from long marches, and low rations.

Human experiments with insect vectors. The world-wide distribution of the disease makes insect transmission unlikely, and the waves of incidence do not coincide with any exacerbation of insect pests. The association of many of our patients with horses has been commented on, but piroplasmosis was excluded. Apart from ticks (the vectors of piroplasmosis) the horse-fly was always abundant. Fleas were never mentioned by patients, but bed-bugs were frequently spoken of. To exclude transmission by bed-bugs, specimens were obtained from the station in which most cases of hepatitis arose, and after starvation for various periods were applied under a watch-glass to the abdomen of cases of infective hepatitis for 12 hours to ensure biting. After various intervals of starvation the bed-bugs were then applied to the abdomen of volunteers, and some of the parasites were also crushed on the skin. All these experiments were negative.

III. THE PATHOLOGY OF HUMAN INFECTIVE HEPATITIS

(In association with Major J. L. DALES, R.A.M.C.)

Historical. The comparative rarity of death from infective hepatitis accounts for the paucity of pathological descriptions. Probert (1938) in a fatal case after the administration of measles convalescent serum, found lobular necrosis of the central type and replacement of the outer zones of the lobules by fibrous tissue. Iversen and Roholm (1939 *a, b*) described a method of 'aspiration biopsy' of the liver and discussed 'the changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies'. They reported a diffuse hepatitis characterized by a destruction of the trabecular structure of the lobule and degeneration of the liver cells in sharply defined foci of variable size, with an inflammatory reaction, chiefly mononuclear, situated in the periportal spaces and to a lesser extent around the central veins. There was also a thickening and collagenization of the reticulin fibrils, and an actual increase in the number of fibrils; this connective tissue change was most marked around the central vein, whence it spread between the liver cells, but also occurred around the periportal

space. The interlobular bile-duets were normal, but bile thrombi were sometimes present in the bile capillaries. The hepatitis was pronounced in the first week and as a rule subsided within a month after jaundice appeared. The theory of a catarrhal pathogenesis was not tenable, and it was supposed that a process of haematogenous origin was involved. As a rule the hepatitis resolved, leaving only a slight or moderate increase in fibrous tissue. In three cases the increase was considerable, suggesting cirrhosis. The lesion in acute necrosis of the liver is fundamentally of the same type, but more pronounced. Two of their cases were chronic alcoholics, and five had been treated with salvarsan, and they conclude that salvarsan jaundice as a rule is an acute infective hepatitis. Soffer (1937) expressed the same view about salvarsan jaundice, as also did Cullinan (1939).

Personal observations. Our own observations in the present war concern autopsy material from four fatal cases of acute hepatitis, none from our own clinical series, and all with rather different clinical courses. In addition, we obtained biopsy material from a non-fatal case operated on for an intercurrent subacute appendicitis. Our thanks are due to Major J. Murray Black, Major W. A. Oliver, and Major H. K. Fidler for some of our material. A brief note of the clinical histories is given first, and the pathology considered afterwards.

Case 1. Typical mild infective hepatitis with the usual course until the 10th day, when sudden symptoms of acute appendicitis supervened. Immediate appendicectomy, and a piece of liver removed at operation. Post-operative course was concurrent with recovery from hepatitis.

Case 2. Mild infective hepatitis with two abnormal features—continuance of pyrexia for five days after icterus appeared, and late onset of liver enlargement. On the 12th day a sudden subarachnoid haemorrhage supervened, with much blood in the cerebrospinal fluid on lumbar puncture. Died on 13th day.

Case 3. French prisoner of war, jaundiced on admission to hospital, who gave a poor history and had no knowledge of the duration of his illness. Liver and spleen enlarged throughout. Seven days after admission vomiting and stupor supervened, and the urine contained albumin and blood but no casts. Died next day.

Case 4. Moderately severe infective hepatitis with increasing icterus. On 39th day of illness vomiting (with blood in vomit) and subcutaneous haemorrhages. Died same day.

Case 5. This soldier was formerly a brewer's drayman. Contracted syphilis in Egypt earlier in the war and had 11 injections (drug unknown) before developing jaundice. Was admitted under our care on 63rd day of illness, dangerously ill, with ascites, diminished liver dullness, olive-green jaundice, and mental disturbance. Became comatose and vomited blood. Died on 74th day. In his unit in Egypt many cases of acute infective hepatitis were occurring when he fell ill.

Pathology. Macroscopic. In Cases 1, 2, 3, and 4 the liver was not greatly altered in size, but in Case 5 it was diminished to two-thirds. In Cases 1

and 2 the liver showed a finely granular appearance on section, with yellow lobules standing out from a general yellowish background. In Case 2 the damage was far more extensive histologically than was expected from the naked eye appearance. In Case 3 the cut surface showed an irregular pattern of reddish-pink and yellow areas. In Case 4 the right lobe was reported to be greenish-yellow, and the left lobe soft and light brown. In Case 5 the liver was reduced to two-thirds in size, and the tissue was soft, friable, and yellowish brown.

Histology. The microscopic changes in Cases 2, 3, 4, and 5 were similar, and were those of subacute necrosis (yellow atrophy) in varying stages. No mitotic figures or evidences of regeneration were observed. The changes in the biopsy material from Case 1 are worth separate description. They consisted of early degeneration in cells at the centre of the lobules, shown by swelling, rounded shape, and diminished intensity of staining; all the degenerating cells showed numerous yellow particles of bile in the cytoplasm; the peripheral cells were normal; greatly increased cellularity of the portal tracts, with lymphocytes and mononuclear cells predominating; Azan staining showed the presence round the central vein of the lobules and in the portal tracts of the hyperplasia of reticulin fibrils described by Iversen and Roholm (1939 *a, b*).

Other pathological changes. In two patients extensive haemorrhages were found, and among the areas involved were the subcutaneous tissues, pleura, peritoneum, mediastinum, lungs, heart muscle, subarachnoid space, spleen, kidney, and stomach. The biliary tract was particularly examined in two cases, but nothing abnormal was found macroscopically or microscopically. The enlarged spleen was examined in four cases, but nothing beyond intense congestion of the sinusoids (and areas of haemorrhage in one instance) was found. In two cases the heart-muscle showed multiple small foci of haemorrhage and degenerative changes in the walls of blood-vessels. The main conclusion arrived at from the pathological study is that a generalized infection damages blood-vessels, leading to haemorrhages, and especially to liver damage resulting in necrosis.

Summary and Conclusions

1. An epidemic of infective hepatitis is described in soldiers serving in the Middle East. The work is presented in three parts, clinical, experimental, and pathological.

2. The work on soldiers has been amplified by correlation with the previous experiences of civilian observers in Palestine, in which the following points seem important:

(a) The disease in a mild form is common in children in Palestine. One attack leads to immunity, so that few native adult sufferers are seen.

(b) Each immigration of settlers furnishes a new non-immune population, and is followed within a few months by fresh cases of hepatitis, both in children and adults.

The arrival of our troops provided the same set of circumstances, and it is obvious that the mixing of new with seasoned troops may lead to fresh outbreaks.

3. The minimum incubation period is about 32 days, but in many patients is obviously much longer. It is suggested that the incubation period is determined by some additional factor which renders the liver susceptible, such as another disease (Sand-fly fever in Palestine), or chill, fatigue, and low diet in field operations.

4. No proof is provided, but the infection is believed to be a virus. Attempts to transmit the disease by insect vectors were negative, and direct spread by droplet infection at close quarters requires further investigation.

5. Experiments on the direct transmission of the disease are recorded. These were negative in all animals available, but positive in soldier volunteers. It is admitted that the human experiments were by no means complete and free from possible error, but the reason for their termination is explained.

6. The importance of treating the condition as a serious liver disease is emphasized. In all our patients jaundice of varying degree was present, but other evidence from Palestine seems to show that jaundice is not essential and that a subdivision into hepatitis *cum ictero* and *sine ictero* may be justified.

7. The pathology of four fatal cases, and of a biopsy specimen of liver obtained at operation, are discussed.

Our thanks are due to many Officers of the Army Medical Service in the Middle East whom we are unable to name personally, but especially to the D.D.M.S. British Forces in Palestine and the Consultant Physician, Middle East Forces. Particularly we wish to mention Sister Scott-White, Q.A.I.M.N.S. (R), whose services in the hepatitis ward during the investigation were invaluable. We also thank the Commanding Officers, A.D.M.S., and Regimental Medical Officers of the Cavalry Division from which our volunteers were obtained, and we cannot sufficiently express our gratitude to the volunteers themselves. Valuable assistance was provided by many civil sources in Palestine, and we wish to acknowledge here the help of the Public Health Laboratories and Medassah Hospital, Jerusalem, and the Hospitals at Petah Tikvah and Jezreel. Lastly, we wish to thank Lieut. R. Fischel, R.A.M.C., for the preparation of the coloured drawings for the illustrations.

Editorial Note.—This paper is an abridged version of a longer report which cannot in the present circumstances be published in full. As the author is in a distant theatre of war and in view of the topical interest of his observations, it is considered advisable to publish the main findings although the author has not had the opportunity of seeing a proof.

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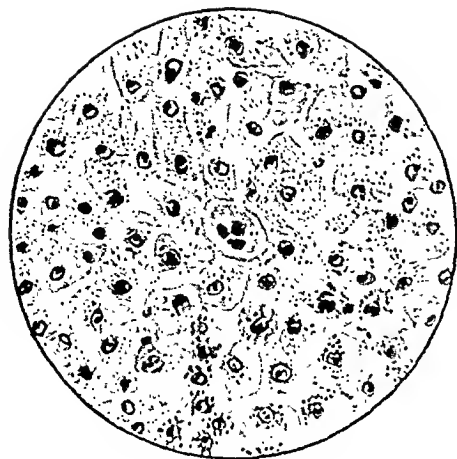


FIG. 3. CASE 1.—Liver showing accumulation of bile-pigment in cells of central portion of lobule (haematoxylin and eosin, x 750).

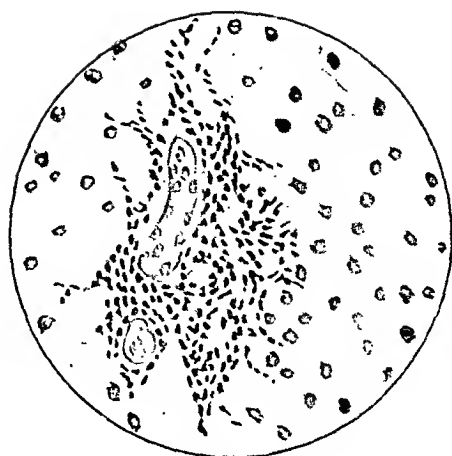


FIG. 4. CASE 1.—Liver showing cellular infiltration of periportal tissues (haematoxylin and eosin, x 750).

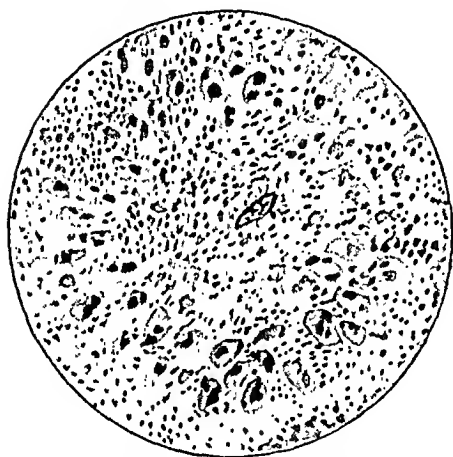


FIG. 5. CASE 3.—Liver showing marked degeneration of central cells of lobule, with widespread infiltration with inflammatory cells (haematoxylin and eosin, x 325).

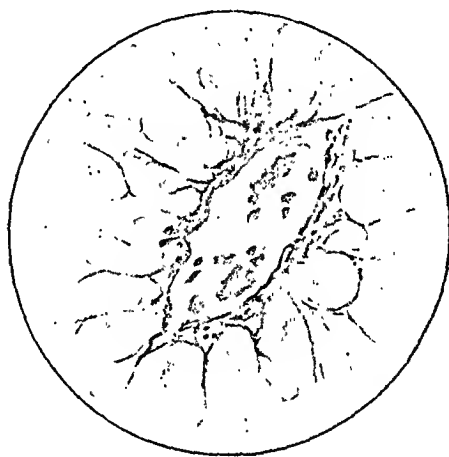
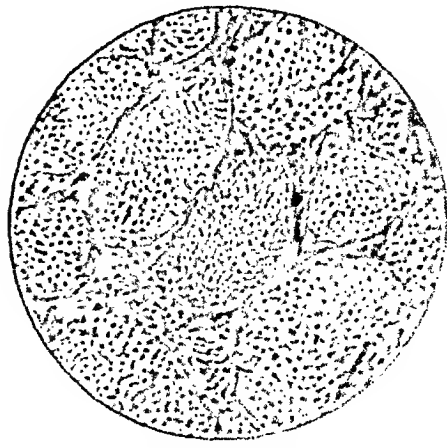
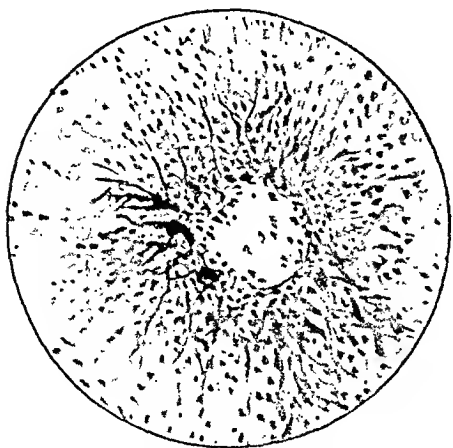


FIG. 6. CASE 1.—Liver showing commencing intercellular reticulin hyperplasia spreading from central vein of lobule (Azan, x 750).



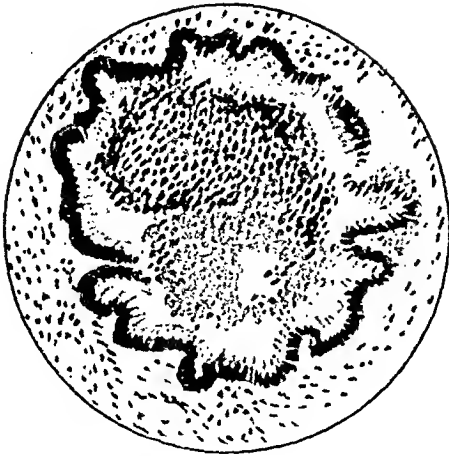


FIG. 9. CASE 2.—Bronchiole showing lumen filled half with inflammatory cells and half with red blood-cells; also peribronchiolar infiltration with inflammatory cells (haematoxylin and eosin, x 750).

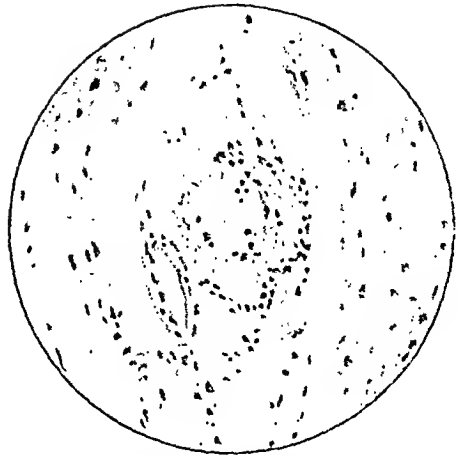


FIG. 10. CASE 2.—Heart showing degeneration of arteriole with inflammatory cells in wall of vessel and surrounding it (haematoxylin and eosin, x 750).

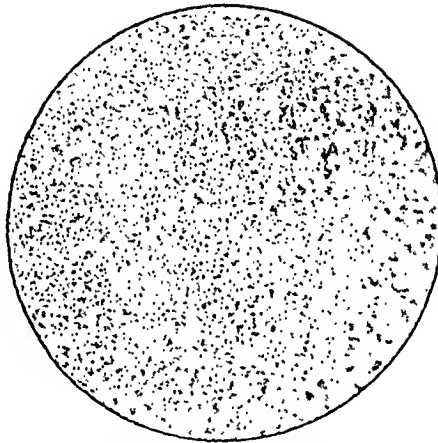
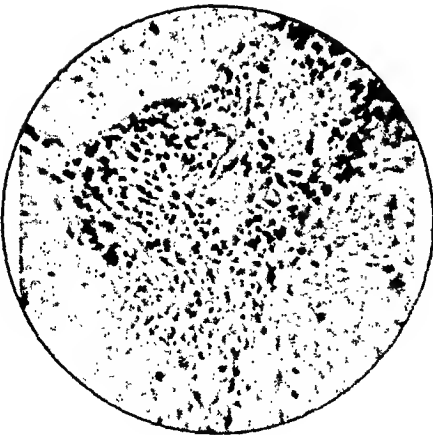


FIG. 11. CASE 2.—Low-power photomicrograph of liver, showing destruction of lobules except for scattered small groups of liver cells at the periphery.



ELLIPTOCYTOSIS IN MAN

associated with

HEREDITARY HAEMORRHAGIC TELANGIECTASIA¹

By JOHN B. PENFOLD AND JOHN M. LIPSCOMB

(From the London Hospital)

With Plate 17

WE have recently had the opportunity of studying a Jewish family living in London whose members show a combination of two rare abnormalities, one of the blood and one of the vascular system. The former, elliptocytosis (oval red cells), is an inherited abnormality which has not previously been described in this country, although the number of cases reported from America and Continental Europe is now considerable. The latter, hereditary haemorrhagic telangiectasia, has been fully described in this country and owes its definition to English writers.

Human Elliptocytosis

This anomaly of human red blood-cells which has been variously called 'elliptocytosis', 'ellipsocytosis', 'ovalocytosis', 'ellipsocythaemia', and 'cameloid blood', presents a picture of red cells which instead of being circular bi-concave disks are predominantly oval or elliptical in shape. The non-mammalian vertebrates, and among mammals the camelidae only, have cells of this shape. The condition is not to be confused with the alteration in the shape of the red cells which is found in anaemia, nor with the sickle-cell trait. From the latter it differs in several distinct features.

The frequency of its occurrence can be judged from the fact that since it was first described over 350 cases have been reported, while McCarty (1934) states that she has seen it four times in the routine examination of 10,000 blood samples. The lack of English case reports suggests that it may be even rarer in this country. The literature has recently been reviewed by Wyandt, Baneroff, and Winship (1941), and only the more important contributions need be mentioned here.

Elliptical red cells were first found by Dresbach (1904) in a healthy mulatto. He later described (Dresbach, 1905) how his specimens were seen by Ehrlich, Arneth, Ewing, and Ewald, all of whom considered that the abnormality was developmental. That it might be hereditary was first suggested by Bishop's (1914) cases. Huek and Bigalow (1923) differentiated

¹ Received December 3, 1942.

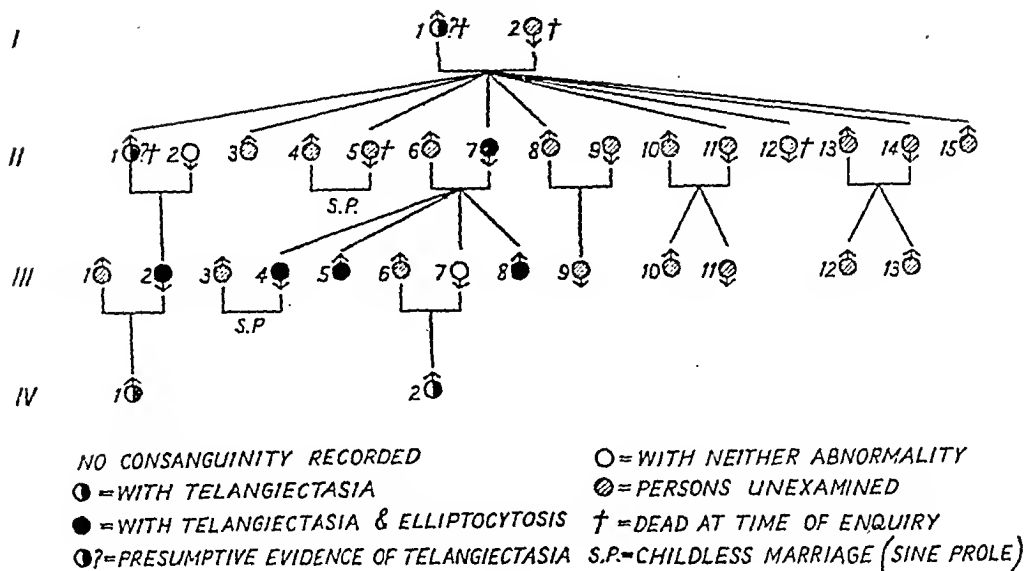


FIG. 1

Case I. 1, is remembered to have bled freely from the nose.

Case II. 1, died aged 25 years within 24 hours of the onset of an acute cerebral condition resembling subarachnoid haemorrhage. No record was obtainable.

Case II. 7, aged 54 years, first attended the London Hospital in 1934 with a history of epistaxis for years, gradually becoming severe, with recent pallor, weakness, and dyspnoea. Small telangiectases found on lips, tongue, and nostrils, spider-like lesions on cheeks, few on chest, back, abdomen, and arms, and under nails near finger tips. Blood count then showed red cells 2,200,000 per c.mm., haemoglobin 55 per cent. Spleen not felt. Oval cells abundant in present investigation.

Case III. 2, aged 32 years, has suffered from epistaxis for many years; it was already troublesome by the age of 17 years, when her nose was repeatedly cauterized, and is now growing steadily worse. She attended the London Hospital in 1927 during her first pregnancy, on account of cough, haemoptyses up to 2 oz., and daily epistaxis. She was later admitted with eclamptic convulsions for which caesarian section (live baby) and sterilization were performed. In 1935 she collapsed in the street; a period of faintness and aphasia was followed by unconsciousness. Attacks of this kind, not always ending in unconsciousness and never attended by tongue-biting or incontinence, have occurred frequently since then. Five years ago she was admitted to one hospital on account of haemoptysis and later to another with 'influenza' and jaundice. Recently admitted to the London Hospital with symptoms of pyelitis. Small bright red telangiectases seen on lips, chest, and palate; none seen in nose. No jaundice, spleen not palpable. While under treatment she had an attack of aphasia without loss of consciousness; next day there was headache and neck-rigidity, but lumbar puncture was unsuccessful. Her blood contains many oval cells and evidence of abnormal haemolysis is present.

Case III. 4, aged 25 years, rarely bleeds from the nose, but gives a history of three attacks of jaundice, one in the London Hospital (1929) and a second in the London Jewish Hospital (1939), neither of which can be satisfactorily confirmed. She was admitted to the London Hospital in 1942 for a minor gynaecological operation. On that occasion she had obvious jaundice and the spleen was easily palpable. The blood contained plentiful oval cells and there was evidence of haemolysis and regeneration. There were minute telangiectases on the hard palate and alveolar margins, and a few on the lips.

Case III. 5, aged 23 years, first complained of blood-stained sputum and occasional moderate haemoptyses two years ago. Epistaxis very frequent. In January 1940 further haemoptysis; in hospital one month. In April 1941 haemoptysis of half-pint outside the London Hospital. X-ray showed small shadow in lower zone of right lung, but sputum was consistently negative for tubercle bacilli. Bronchoscopy and lipiodol

revealed no abnormality. Blood counts at that time showed moderate polycythaemia, red cells up to 6,130,000 per c.mm., haemoglobin up to 135 per cent., and the spleen was palpable. Present investigation shows abundant oval red cells and evidence of increased haemolysis. Chronic cough with blood-staining persists, epistaxis is frequent, and a small telangiectasis is now visible on the nasal septum.

Case III. 7, aged 21 years, has no history of bleeding, no visible telangiectases, and a normal blood film.

Case III. 8, aged 19 years, attended the London Hospital on account of free nose-bleeding of recent onset. One slightly raised spider telangiectasis (about 1.5 cm. in diameter) on left cheek; none seen in nose or mouth. Spleen not felt. Blood contains oval cells and shows signs of abnormal haemolysis.

Case IV. 1, aged 14 years, has occasional epistaxis. There are small telangiectases on lips and tongue. The spleen cannot be felt and the blood is normal.

Case IV. 2, aged 2 years, whose mother appears normal, has one small spider telangiectasis on nose, but no bleeding. Blood not examined.

oval cells from sickle cells by observing that no change in their shape occurred when they were watched for some time in a wet preparation. They also observed the fate of transfused oval cells and could find none in the normal recipient after two months. Up to 1929 only seven references to the condition, comprising 15 cases, were available (Cheney, 1932), but from that time interest was stimulated by Hunter and Adams (1929, 1932) in America and van den Bergh (1931) in Holland, who investigated different branches of the same family. It was then established that the condition was hereditary, transmitted as a Mendelian dominant, manifested from birth, and present in males and females equally. Van den Bergh (1931) showed that the oval shape was an intrinsic property of the cells, and he was the first (van den Bergh, 1928) to record associated icteric phenomena. Terry, Hollingsworth, and Eugenio (1932) performed necropsies on two cases of elliptocytosis dead from other causes, and found no abnormality referable to or connected with oval cells. They noted that the nucleated red cells of the marrow were round. Bernhardt (1928) and Cheney (1932) found no oval cells in sternal puncture material from patients in whose peripheral blood many such cells were found. Grzegorzewski (1933) found evidence of abnormal haemolysis in six of 14 cases. McCarty (1934) suggested that oval cells were older and therefore more fragile than normal cells. Stephens and Tatelbaum (1935) reported an associated polycythaemia. Florman and Wintrobe (1938) observed that the change from round to oval forms began at the reticulocyte level, and Strauss and Daland (1937) noted that during a vigorous reticulocytosis after haemorrhage in a patient with oval cells the reticulocytes were round. Transfusion experiments by Viseher (1938) showed that the survival time of oval cells in the normal recipient was much shorter than that of normal cells; he found high reticulocyte counts and increased bone marrow activity in 12 apparently healthy patients with elliptocytosis. Giffin and Watkins (1939) described three members of a family in whom oval cells were associated with haemolytic icterus. Recently, Wyandt, Bancroft, and Winship (1941) in addition to an extensive review of the subject reported 86 further cases.

Hereditary Haemorrhagic Telangiectasia

The three indispensable factors in this condition are implicit in its title and were fully described by Osler in 1901 and 1907, and Weber in 1907. Since then the literature has assumed considerable proportions and has been needlessly confused by many reports of variations of the syndrome. The lesion is an angio-hamartoma or error of capillary development. Typically it is a spider-like aggregation of dilated venules upon the skin or mucous membranes, usually flat but often with a central raised purplish nodule of distended capillaries. The more raised its centre the more it tends to bleed, and in this tendency lies its only clinical significance. Osler (1907) clearly defined the hereditary type and differentiated it from the various bleeding diseases and from telangiectasia secondary to diseases of the liver.

The lesions are commonly found on the lips, nose, cheeks, buccal mucosa, palate, gums, tongue, and on the nasal septum and turbinates. They have been described in many other sites, and to some of these descriptions specific reference will be made later. The condition is progressive with age. As a rule haemorrhages occur before the lesions are noticed, but the converse is also found. Madden (1934) stated that telangiectases may be present from birth, while each of a group of young patients whom Fitz-Hugh (1923) examined by rhinoscopy showed intranasal lesions. Haemorrhage rarely begins before puberty and is seldom serious before the fourth decade. The most severe cases we have seen have been in middle-aged women; in one of these (not of the family here described) old lesions grew bigger and new appeared where none had been present before. The only related abnormality of the blood is a secondary anaemia after haemorrhage from the lesions; this may be severe enough to require repeated transfusions. Death has been described from epistaxis and more rarely from pharyngeal haemorrhage (Fitz-Hugh, 1923) and cerebral haemorrhage (Mekie, 1927).

Haematological Findings

In general it may be stated that those members of the family showing elliptical red cells had in addition signs of haemolytic icterus without an increase in fragility. Three members showed a slight degree of secondary anaemia, while one had an increase in red cells. In an attempt to obtain a clearer idea of the degree of elliptocytosis, the red cells were grouped into four classes, slight, moderate, and severe elliptocytosis, and normal cells (Plate 17, Fig. 2).

Percentage counts were done on dry films and wet films at once, 48 hours later, and 96 hours later. The results are shown in Table I.

It will be seen from Table I that five persons had over 90 per cent. of oval red cells in their blood, and although the percentage varied from person to person it seemed to be quite constant for the individual concerned. Further points noticed were that the wet film gave consistently higher percentages than the dry film and that the change in the wet count on

TABLE I

Percentages of Oval Red Cells in the Family Members

MEMBERS SHOWING ELLIPTOCYTOSIS

Case	Dry film				Wet film at 0 hours				Wet film at 48 hours				Wet film at 96 hours			
	Total	Slight	Moderate	Severe	Total	Slight	Moderate	Severe	Total	Slight	Moderate	Severe	Total	Slight	Moderate	Severe
II. 7	78.5	21	34.5	23	100	14	39.5	46.5	99.5	15.5	38.5	45.5	99.5	12	40.5	47
III. 2	86.5	29	42	15.5	92.5	24	54.5	14	92.5	23	47.5	22	93.5	19	43	31.5
III. 4	97.5	11.5	26	60	99.5	13	36	50.5	100	10	32	58	99.5	13.5	30.5	55.5
III. 5	92	27	50.5	14.5	97	28	60.5	8.5	96.5	27	58	11.5	97.5	30.5	54.5	12.5
III. 8	97	18.5	48.5	30	98.5	19	46.5	33	99	22	47.5	29.5	99.5	17.5	58.5	23.5
MEMBERS NOT SHOWING ELLIPTOCYTOSIS																
II. 2	1.5	1.5	0	0	6.5	4.5	2	0	27.5	20.5	7	0	32.5	22.5	9.5	0.5
III. 7	18	16	2	0	21.5	19	2.5	0	12	9.5	2.5	0	14	9.5	4.5	0
IV. 1	10.5	6.5	3.5	0.5	10	6.5	3	0.5								

[161]

TABLE II

Further Haematological Findings in Members with Elliptocytosis

Case	Date	Percentage of oval cells in wet film	Red cells in millions per c.mm.	Haemoglobin per cent.	Colour index	Haemato- cyt	Blood group	Percentage of reticulo- cytes	Van den Bergh reaction	Corrected sedi- mentation rate in 1 hr.
II. 7	23.11.41	100	4.06	76	0.95	30	O	4.6	Delayed direct 1.5 mg. %	5 mm.
III. 2	21.9.41	92.5	5.28	102	0.96	30	A	1.8	Negative	12 mm.
	27.11.41	—	5.14	114	1.11	35	—	4.2	—	—
III. 4	27.42	93.0	3.98	82	1.03	—	—	3.6	Delayed direct 1.25 mg. %	—
	23.11.41	99.5	4.56	92	1.02	35	O	6.4	Delayed direct 3.2 mg. %	—
III. 5	26.9.42	—	3.87	89	1.04	38	—	5.2	Delayed direct 4 mg. %	28 mm.
	15.4.41	—	5.50	135	1.2	—	—	—	—	—
	6.8.41	—	6.13	119	0.97	—	—	—	—	—
	12.3.42	—	5.86	122	1.06	51	O	0.8	Delayed direct 1.5 mg. %	2 mm.
	27.42	89	5.84	118	1.01	—	—	1.3	Delayed direct 1.0 mg. %	—
III. 8	29.9.41	99.5	5.10	112	1.09	41	O	1.6	Delayed direct 6 mg. %	2 mm.

keeping was not significant (cf. sickle-cells). We believe that the count done on the dry blood film is not reliable, as the number of oval cells varied with the film, particularly with its thickness. The oval cells were most numerous where the film was thickest, becoming fewer as the film became thinner.

Blood from three of the subjects was diluted 200 times in hypertonic (1.2 per cent.) and hypotonic (0.6 per cent.) saline, and daily counts of the total and oval red cells were made. In the hypertonic saline (Plate 17, Fig. 3) the absolute number of oval red cells diminished to a minimum about the third or fourth day, rising again later (about the fifth or sixth day) to a figure not as high as the original. There was a diminution in the total count, gradual at first and more rapid later. Corresponding to the absolute diminution of the oval cells about the third or fourth day there was at that time an absolute increase in the cells which appeared round. Similar results were obtained in the hypotonic saline solution. These observations showed that the oval shape could be changed by alteration in the physical characters of the medium.

Further haematological studies were carried out, and the following investigations were found normal—red cell fragility test, total white cell count, differential white cell count, platelet count, bleeding time, coagulation time, and Wassermann and Kahn reactions. The remaining investigations are shown in Table II.

Discussion

Genetic observations. The hereditary nature of elliptocytosis was first suggested by Bishop's cases in 1914, and since then ample evidence has accumulated to confirm this view. Wyandt, Bancroft, and Winship (1941) in their review found 64 family histories comprising 246 cases. The pedigree presented in the present paper is unfortunately small, but as far as it goes is in complete agreement with the accepted view that elliptocytosis is inherited according to Mendelian laws as a dominant character.

The pedigree of our cases reveals another mesoblastic defect, hereditary haemorrhagic telangiectasia. This anomaly is also inherited as a Mendelian dominant and is much more commonly reported than elliptocytosis. These are the first cases to be described in which the two abnormalities appear together, although other defects have been reported in association with elliptocytosis (Günther, 1928; Rosenow, 1933). Since genetic linkage has been suggested by the authors in some of these cases it is worth considering this in more detail. The genetic linkage of two or more characters indicates that the genes controlling them exist upon the same chromosome. It follows that except in the rare cases where 'crossing over' occurs the two characters will always be found together. In fact this almost invariable association of two characters is the chief clue indicating their linkage. Cases have been described of elliptocytosis associated with oxycephaly (Günther, 1928) and defects of the lateral incisors (Rosenow, 1933). In neither of these cases is the incidence of linkage sufficiently high to warrant the assumption that it

is genetic in the sense defined above. The association of anomalies in our own cases may very well be fortuitous since both are inherited as Mendelian dominants; in any event no valid conclusion can be drawn from such small numbers.

We take the view that the genes here involved may be of relatively recent origin and still unstable. Such instability manifests itself in mutations which are probably much more common than is generally realized. It is a fact that many recognized mutations are retrogressive in character, and many may be considered atavistic, although this is of course beyond proof. It is suggested that the appearance of elliptocytosis in association with hereditary haemorrhagic telangiectasia could be satisfactorily explained if both were regarded as atavistic mutations. This view has been put forward by others in connexion with elliptocytosis and rests chiefly on the fact that most vertebrates lower than the mammals have oval erythrocytes. This is evidently the primitive type of red cell. It is invariably found in one group of mammals, the camelidae, and its presence here might be explained as a mutation which occurred in the common ancestor of this group. On this supposition it seems possible that a similar mutation might occur in other mammalian groups.

It is not impossible that telangiectasia is also a reference back to an amphibian state in which the mucous membranes of mouth and throat regions and the skin are accessory breathing surfaces and therefore highly vascular. Terry, Hollingsworth, and Eugenio (1932) claimed that elliptocytosis might furnish a link with the marine vertebrates, and perhaps telangiectasia might also be regarded in this light. Such suggestions on the origin of these anomalies can never be proved and have no practical value. On the other hand the observations on the type of inheritance they show are based on extensive pedigrees and are therefore valid.

Hereditary haemorrhagic telangiectasia. Four of our cases conform to the classical standards. Three others exhibit part or parts of the syndrome and are young enough to develop the remainder in years to come. Several points of interest emerge from the case histories. Case II. 7 is classical. Case III. 5 coughed up blood, and extensive investigations revealed no tuberculous infection; at bronchoscopy no telangiectases were seen, but this factor in the aetiology was unsuspected at the time and the lesions were not deliberately looked for. A remarkable family with hereditary haemoptysis was described by Libman and Ottenberg (1923), but bronchoscopy on two members revealed no telangiectases. Fitz-Hugh (1923) described haemorrhage from the throat, and in 1896 Ullmann had found bronchial telangiectases at necropsy, but as far as we can ascertain no lesions have ever been seen beyond the epiglottis (Weber, 1907) in the living subject. Case III. 2, in addition to the classical picture with early onset and multiple haemoptyses, manifested strange attacks of aphasia, headache, and neck rigidity. Lumbar puncture after such an attack unfortunately failed. Her father, Case II. 1, died at the age of 25 years from an unspecified cerebral condition resembling subarachnoid

keeping was not significant (cf. sickle-cells). We believe that the count done on the dry blood film is not reliable, as the number of oval cells varied with the film, particularly with its thickness. The oval cells were most numerous where the film was thickest, becoming fewer as the film became thinner.

Blood from three of the subjects was diluted 200 times in hypertonic (1.2 per cent.) and hypotonic (0.6 per cent.) saline, and daily counts of the total and oval red cells were made. In the hypertonic saline (Plate 17, Fig. 3) the absolute number of oval red cells diminished to a minimum about the third or fourth day, rising again later (about the fifth or sixth day) to a figure not as high as the original. There was a diminution in the total count, gradual at first and more rapid later. Corresponding to the absolute diminution of the oval cells about the third or fourth day there was at that time an absolute increase in the cells which appeared round. Similar results were obtained in the hypotonic saline solution. These observations showed that the oval shape could be changed by alteration in the physical characters of the medium.

Further haematological studies were carried out, and the following investigations were found normal—red cell fragility test, total white cell count, differential white cell count, platelet count, bleeding time, coagulation time, and Wassermann and Kahn reactions. The remaining investigations are shown in Table II.

Discussion

Genetic observations. The hereditary nature of elliptocytosis was first suggested by Bishop's cases in 1914, and since then ample evidence has accumulated to confirm this view. Wyandt, Baneroff, and Winship (1941) in their review found 64 family histories comprising 246 cases. The pedigree presented in the present paper is unfortunately small, but as far as it goes is in complete agreement with the accepted view that elliptocytosis is inherited according to Mendelian laws as a dominant character.

The pedigree of our cases reveals another mesoblastic defect, hereditary haemorrhagic telangiectasia. This anomaly is also inherited as a Mendelian dominant and is much more commonly reported than elliptocytosis. These are the first cases to be described in which the two abnormalities appear together, although other defects have been reported in association with elliptocytosis (Günther, 1928; Rosenow, 1933). Since genetic linkage has been suggested by the authors in some of these cases it is worth considering this in more detail. The genetic linkage of two or more characters indicates that the genes controlling them exist upon the same chromosome. It follows that except in the rare cases where 'crossing over' occurs the two characters will always be found together. In fact this almost invariable association of two characters is the chief clue indicating their linkage. Cases have been described of elliptocytosis associated with oxycephaly (Günther, 1928) and defects of the lateral incisors (Rosenow, 1933). In neither of these cases is the incidence of linkage sufficiently high to warrant the assumption that it

is genetic in the sense defined above. The association of anomalies in our own cases may very well be fortuitous since both are inherited as Mendelian dominants; in any event no valid conclusion can be drawn from such small numbers.

We take the view that the genes here involved may be of relatively recent origin and still unstable. Such instability manifests itself in mutations which are probably much more common than is generally realized. It is a fact that many recognized mutations are retrogressive in character, and many may be considered atavistic, although this is of course beyond proof. It is suggested that the appearance of elliptocytosis in association with hereditary haemorrhagic telangiectasia could be satisfactorily explained if both were regarded as atavistic mutations. This view has been put forward by others in connexion with elliptocytosis and rests chiefly on the fact that most vertebrates lower than the mammals have oval erythrocytes. This is evidently the primitive type of red cell. It is invariably found in one group of mammals, the camelidae, and its presence here might be explained as a mutation which occurred in the common ancestor of this group. On this supposition it seems possible that a similar mutation might occur in other mammalian groups.

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haemorrhage. The occurrence of cerebral telangiectases as suggested by Goldstein (1921), Mekie (1927), and Fitz-Hugh (1923) is purely speculative and no evidence of their existence has ever been brought forward which can compare with Hurst, Hampson, Plummer, and Yates's (1932) sigmoidoscopic findings or Ullmann's (1896) post-mortem report. Nevertheless, the inferences which may be drawn from Cases II. 1 and III. 2 are highly suggestive.

Human elliptocytosis. The main interest of our five cases with oval cells lies in the finding of icteric phenomena in all of them. The results of van den Bergh reactions and reticulocyte counts are shown in Table II. In addition Case III. 4 was observed in hospital with clinical jaundice and splenomegaly, Case III. 2 gave a history of one attack of jaundice, and on one occasion splenomegaly was noted in Case III. 5. It is our view that in spite of a significant amount of evidence available in the literature the importance of this association between elliptocytosis and abnormal haemolysis has been ignored. This mistake has arisen in part from the anxiety of earlier writers to establish elliptocytosis as a condition in its own right and to separate it from the poikilocytosis of severe anaemias and from the sickle-cell trait.

In 1938 Mason, contributing a section on oval red cells to Downey's *Handbook of Haematology*, gave special consideration to the cases of van den Bergh (1928), Lawrence (1931), and Hunter and Adams (1932) because they showed unexplained anaemia. He wrote 'In a few instances (of elliptocytosis) some degree of anaemia has been present and in a very few patients the anaemia, of haemolytic type but of unknown aetiology, has been severe. Perhaps an analogous situation is encountered in sickle-cell anaemia and haemolytic icterus. In each of these maladies the trait is much more frequent than the active phase of the disease. . . . These three hereditary defects of haemopoiesis have much in common.' These words of Mason's are certainly prophetic although further examination of the evidence upon which he based his hypothesis shows it to be inadequate. Van den Bergh's (1928) case and his own, both with oval cells, anaemia, and jaundice, are authentic; in contrast to these the anaemias described by Lawrence and by Hunter and Adams are hardly admissible in this context. Although the available material was limited we welcome the conclusion which he drew from it.

Our own examination of the reported cases has shown that of all the known examples of elliptocytosis, numbering between 350 and 400, about 50 showed some signs of abnormal haemolysis. This gives an incidence of not less than 12 per cent. A few instances may be mentioned. Van den Bergh's (1928) German case was one of the earliest; elliptocytosis was associated with jaundice and splenomegaly, but the fragility was normal, and although the icteric signs disappeared after splenectomy the oval cells were unchanged. Mason's (1938) Case I had attacks of weakness which twice required transfusion; he was found to be pale and icteric with traces of bile and urobilin in the urine and 2.5 per cent. of reticulocytes; three of his

mother's cousins had died of severe unexplained anaemia before the age of 30 years. Giffin and Watkins (1939) described a remarkable family with oval cells. The mother showed severe anaemia with jaundice, splenomegaly, and 10·4 per cent. of reticulocytes. The red cell fragility was slightly raised. After splenectomy the symptoms improved, but the fragility and cell shape were unaltered. Her daughter experienced typical haemolytic crises from childhood. On examination there was jaundice, splenomegaly, 6·9 per cent. of reticulocytes, and evidence of gall stones. The fragility was slightly increased. After splenectomy the symptoms disappeared, but the oval cells were unchanged. Finally, her son who was without symptoms had a palpable spleen, an increase in the red cell fragility, and a raised serum-bilirubin. These cases bear a close resemblance to the clinical picture of familial acholuric jaundice in its various phases. Carriers of the spherocyte trait are liable to bouts of haemolytic anaemia just as carriers of the sickle-cell trait may experience acute icteric phases. The accumulated evidence strongly supports Mason's postulate of elliptocytosis as an oval-cell trait in which phases that might be termed 'haemolytic elliptocytic anaemia' are liable to occur. A further point of interest is that one of our cases was polycythaemic, a phenomenon noted by Stephens and Tatelbaum in 1935 in eight members of a family with elliptocytosis. Thus it will be clear that any theory of the mechanism of elliptocytosis must take into account the symptomless 'elliptocyte trait', 'haemolytic elliptocytic anaemia', and possibly 'elliptocytic polycythaemia'.

Alterations in the red cells of the types found in spherocytosis, the sickle-cell trait, and Addison's anaemia lead to an increased susceptibility to the destructive effects of the reticulo-endothelial system. It appears that elliptical red cells are susceptible in the same way. In all these conditions the destruction is usually not great and compensation is achieved by a slight and perhaps unobserved increase in erythropoiesis. If the cell destruction becomes greater then it is conceivable that a stage would be reached when red cell formation could no longer keep pace with destruction and a haemolytic anaemia would result. On the other hand, the destruction of red cells may excite a hyperactivity of erythropoiesis with a consequent polycythaemia. As might be expected this is very rare, haemolytic anaemia is more common, and the oval-cell trait without clinical symptoms is commonest of all. It is not easy to understand why these abnormal cells, whether oval, spherical, or sickle-shaped, should be more readily destroyed than normal round cells. The usual red cell fragility test gives no clue to the answer. Although spherocytes are abnormally fragile in serial saline dilutions, the cells of Addison's anaemia, elliptocytosis, and the sickle-cell trait are shown by this test to have a normal or even increased resistance. Obviously this *in vitro* test is no indication of the condition *in vivo*. No direct evidence is forthcoming as to whether an alteration in the shape of the red cell predisposes *per se* to an increased susceptibility to the destructive action of the reticulo-endothelial system. The indirect evidence of haemolysis in such

conditions as acholuric jaundice, sickle-cell anaemia, haemolytic elliptocytic anaemia, and Addison's anaemia strongly supports this view.

On the other hand there is some evidence to show that oval cells are old cells and therefore more liable to destruction. In support of this view, sternal puncture by Bernhardt (1928) and Cheney (1932) has shown that the nucleated red cells of the marrow are round, and other workers (Florman and Wintrobe, 1938; Strauss and Daland, 1937) have seen that the change from round to oval forms takes place at the reticulocyte level. Further, Viseher (1938) has shown by transfusion experiments that oval cells disappear with abnormal rapidity from the blood stream of normal recipients. This disappearance may be interpreted in two ways; either, as McCarty (1934) suggested, the oval cells are old and therefore due for destruction, or they are destroyed by virtue of their abnormal shape which causes them to be trapped in the reticulo-endothelial mechanism through which normal cells would pass. Thus while we have brought forward evidence to show that elliptocytosis can and does cause haemolytic anaemia, the nature of the mechanism is unknown and we can only postulate that the oval cells are destroyed by virtue of their age or of their essential morphological abnormality.

We wish to thank Mr. J. M. Dodd for his suggestions on the genetic aspects of the cases, Dr. P. N. Panton and Prof. S. P. Bedson for helpful criticism, Mr. John King for the photo-micrograph, and Dr. A. E. Clark-Kennedy and Dr. Donald Hunter for permission to publish their cases.

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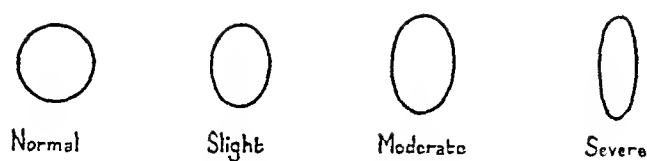


FIG. 2. Standards of Elliptocytosis used

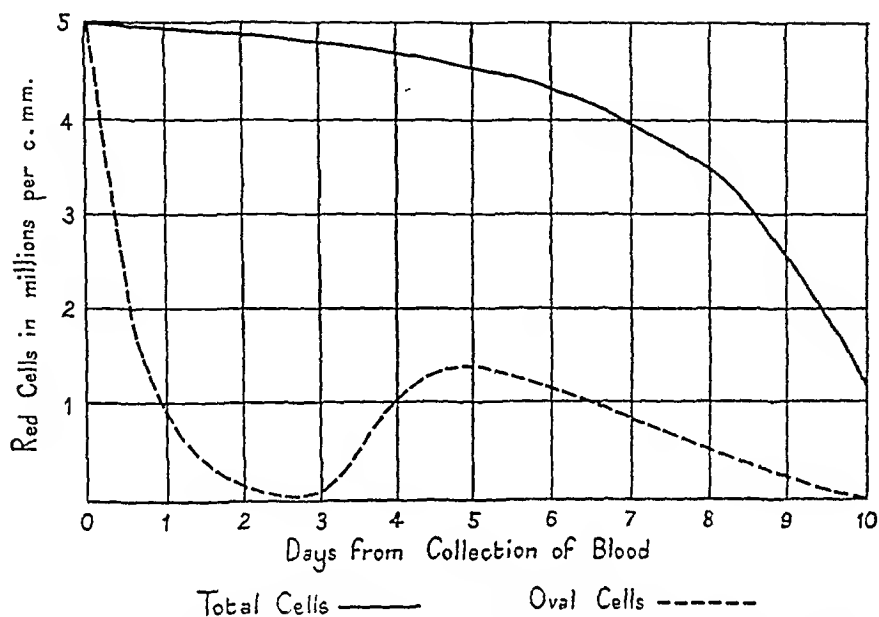


FIG. 3. Reaction of the Oval Red Cells in Hypotonic and Hypertonic Saline



FIG. 4. Dried Blood-film from Case III, 4. (Stained with Leishman and Eosin $\times 640$)



THE PATHOLOGICAL AND CLINICAL FINDINGS IN BLAST INJURY¹

By R. E. TUNBRIDGE AND J. V. WILSON

IN the 1914-18 World War a number of men were found dead without any evidence of external injury. Logan (1939) mentioned a German officer found dead in the act of moving a chess piece, and men found dead inside a concrete pill-box which had been hit but not penetrated by an eight inch shell. Many such cases were found by British, French, and German authorities to have died from carbon monoxide poisoning. In other cases death was attributed to asphyxia. In the light of present day experience it appears that in some at least of these cases death may have been due to the effects of blast. Stokes in a personal communication to Logan (1939) stated that post-mortem examination of such cases revealed evidence of lung haemorrhages and injury to the abdominal organs, lesions found to-day in cases of blast injury. Mott (1917) described the pathological findings in a series of cases where death followed exposure to the blast of high explosive shells. One man had a large haemorrhagic area in the lower lobe of the left lung and both lungs were oedematous, otherwise the abnormal findings were confined to congestion of vessels and minute haemorrhages in the nervous systems. Mott 'attributed death to aerial compression by the high explosives transmitted to the base of the brain with injury or shock to the vital centres'. Accounts of the Spanish Civil War have tended to exaggerate the incidence of deaths attributable to the effects of blast, that is, death without any sign of external injury occurring close to the site of detonation of a bomb, but clinical and pathological records of death from this cause are scanty.

Barcroft (1939) and Zuckerman (1940 *a*) have investigated the effects of the explosive wave or blast following the detonation of bombs and high explosives upon a variety of experimental animals. Zuckerman (1940 *a*) found in animals, suitably protected from the effects of fragments and debris, that with a given charge of explosive the degree of injury depended upon the species of animal used and its distance from the site of detonation. Using a 70 lb. charge, animals situated within 18 feet of the explosion were killed, while those situated more than 50 feet away were uninjured. Of the animals killed, those situated close to the site of explosion were dismembered, whilst those farther away revealed no evidence of external injury. The animals placed 18 to 50 feet from the explosion could be divided into two groups, those nearest to the explosion who died anything from one minute

¹ Received September 9, 1942.

to 24 hours afterwards exhibiting marked respiratory distress, and those farther away which though exhibiting respiratory symptoms, cough, dyspnoea, and blood-stained sputum, recovered without sequelae. All the animals examined had extensive lung haemorrhages, 40 per cent. had abdominal lesions, and evidence of haemorrhage was occasionally found in the ear drums, muscles, and nervous system. Barcroft (1939) recorded similar findings in goats placed within 15 feet of the site of detonation of a 500 lb. bomb. Lung haemorrhages were the principal autopsy finding.

Reports of human deaths attributable to blast injury during the present war have been recorded by Falla (1940), Osborn (1940), Hadfield, Ross, Swain, and Drury-White (1940), Hadfield and Christie (1941), and Zuckerman (1940 *b*). Both Zuckerman (1940 *b*) and Hadfield (1941) stress the difficulty in deciding the primary cause of death in cases injured as a result of bomb explosion. In 30 cases examined by Hadfield (1941) and considered from the history and the clinical evidence to have died from the effects of blast, 13 showed no anatomical evidence of death from this cause, and of the remaining 17 which showed multiple bilateral pulmonary haemorrhages with little or no significant injury to the thoracic wall, four had over 50 per cent. blood-saturation with carbon monoxide. In addition to these fatal cases, the clinical findings have been described in non-fatal cases by a number of observers. Dean, Thomas, and Allison (1940) reported a series of 27 cases in all but two of which there was a history of close exposure to heavy blast. The cases were examined 7 to 10 days after the event; six complained of symptoms related to the chest, 16 showed some abnormal physical signs, and 14 showed abnormal radiographic appearances. Breden, D'Abreu, and King (1942) reported a series of cases with abdominal injuries—haematemeses, lacerations of the bowel, and late abdominal abscess formation—amongst survivors from a convoy attacked by submarines and subjected to trauma from depth charges. Hadfield and Christie (1941) gave a full account of the clinical and pathological findings in a patient with blast injury to the lungs who survived for 51 hours. Stewart, Russel, and Cone (1941) reported having observed a small series of cases exposed to blast which exhibited a variety of neurological abnormalities, and one case had a xanthochromic spinal fluid. Wakeley (1941) stated that he had seen death, haemoptysis, haematemeses, abdominal pain, and diarrhoea amongst men injured in the water by depth charges. Livingstone (1940), Roberts (1940), and Hadfield (1941) refer to the clinical manifestations of blast injury to the lungs.

The material for the present study was taken from military and civil casualties occurring in Malta, more especially from those occurring during the period of intensive bombing from December 1941 to April 1942. The material was in no way selected, being composed of cases seen by us in the ordinary routine or through the kindness of colleagues both civil and military. The statistical survey originally planned has been rendered impossible owing to the destruction of some of our specimens and records through enemy action and to the difficulties associated with continuous bombing attacks,

the impossibility of visiting all the sites within a reasonable time of the incidents, difficulties of communication, interference with electrical supplies, shortage of X-ray films, and the custom of burying the dead within 24 hours of death.

Pathology

The physics of the blast wave has been well described by Zuckerman (1940) and will not be reviewed further in the present article. Hooker (1923) stressed that the principal pathological finding in animals exposed to the effects of high explosives was pulmonary haemorrhage. As we have already pointed out recent observations both in men and animals confirm this observation. Ross (1941) in her review of lung haemorrhage caused by trauma emphasized that the finding of bilateral pulmonary haemorrhages was not pathognomonic of blast injury, as it was also observed in cases of compression asphyxia, asphyxia, and carbon monoxide poisoning. Hadfield described three cases with a blood-saturation of over 50 per cent. of carbon monoxide and extensive bilateral pulmonary haemorrhages, but he considered that the cases had been exposed to blast before inhaling the carbon monoxide. Robb-Smith (1941) reported bilateral pulmonary haemorrhages as a feature of accident cases dying as a result of pulmonary fat embolism. We have been impressed by the frequent finding of evidence of lung haemorrhage in post-mortem examinations of battle casualties where heavy trauma, without necessarily any evidence of blast injury, had occurred. Osborn (1941) attempted to classify the types of haemorrhage found in cases of blast injury and stressed the importance of costophrenic angle pneumonia. In our experience this has been by no means a frequent finding. Wilson and Tunbridge (1943) have shown that the principal seat of haemorrhage is in the deeper portions of the lung and that the areas of subpleural haemorrhage have little significance. Further experience has convinced us that the extent of haemorrhage is not always commensurate with the severity of the exposure to blast.

The occurrence of lung haemorrhage and the finding of emphysema in cases of blast injury led earlier observers to explain the method of action of blast in terms of the lung findings. Three mechanisms have been suggested to explain the method of production of the pulmonary lesions in blast injury.

1. A suction wave following the blast, leading to rupture of the alveolar capillaries (Logan, 1939).
2. Sudden distension of the lungs with air causing rupture of the lung tissues (Barcroft, 1939).
3. Traumatic effect of the blast wave upon the chest wall (Zuckerman, 1940).

Were the lung lesions the only findings it would be difficult to weigh the merits of the different hypotheses. This, however, is not the case, for Zuckerman (1940*b*) found evidence of abdominal haemorrhages in 40 per cent. of experimental animals and also in some animals haemorrhage into the ear drums, the muscles, and the nervous system. Mott (1917) described

haemorrhages in the brain and spinal cord and Wilson and Tunbridge (1943) found evidence of abdominal haemorrhage in 50 per cent. of a series of 12 fatal cases, and in 45 per cent. of another series of cases. Further, injury to abdominal and thoracic organs as a result of the explosion of depth charges has been reported by Wakeley (1941), Gordon-Taylor (1940), and Breden, D'Abreu, and King (1942). The extent of the extrathoracic lesions, amounting in some cases to the rupture of organs, can hardly be explained by the distension or by the suction theories. Zuckerman (1940 *a*) has produced further evidence in favour of the external trauma theory. Animals placed sideways to the blast tended to show more extensive haemorrhages in the side proximal rather than in the side distal to the explosion. Further by covering the animals with a sponge-rubber jacket, he found that the animals so protected showed considerably less haemorrhage than animals similarly placed but not protected.

In analysing the histories of bomb incidents it is often impossible to obtain a reliable and detailed history from which to draw conclusions as to the effect of position, but in the following instance this evidence was available and the post-mortem findings support Zuckerman's views that the lung haemorrhages are more severe on the side nearest the explosion.

Case 1. A Maltese subject, aged 23 years. He was working in the entrance to a gun-pit when a bomb fell less than four yards away. He was situated sideways in the entrance with his right side towards the explosion and he fell into the area of the gun site. He died approximately four hours after the incident. At autopsy examination the whole of the right side of the body was pitted with minute puncture wounds where dust particles had been driven into the skin. Blood was seen in the right ear and the drum was perforated, but there was no evidence of a fracture of the skull. The thorax was intact and there was no evidence of fracture, wound, or laceration. Both pleural cavities contained a few cubic centimetres of slightly blood-stained fluid. The right lung was the seat of extensive haemorrhage involving the whole of the lung substance. The areas of subpleural haemorrhage were on the posterior surface and the areas bordering on the interlobar septum. There were linear markings over the anterior surface corresponding to the ribs. The left lung showed scattered areas of subpleural haemorrhage along the anterior margin of the upper lobe. There were no extensive areas of haemorrhage in the substance of the lung. There were no abnormal findings in the pericardium, heart, or mediastinum. There was some evidence of haemorrhage around the vessels of the upper abdomen and this was more marked in the pyloric region. The liver showed rib markings and bruising on its anterior surface, but there was no evidence of rupture.

The finding of more extensive haemorrhages on the side nearer the explosion is readily explicable if the blast is assumed to act by means of the traumatic effect of the percussion wave on the body surface, but it is not so readily explicable by the distension or suction theories. The presence of haemorrhagic lesions in the upper abdomen could be explained by the distension theory and the transmission of the forces through the diaphragm. Although most frequently found in the upper abdomen the haemorrhages

and other injuries are not confined to this region in blast injuries. Case 2 illustrates not only the severity but also the widespread distribution of the lesions.

Case 2. A British subject, aged 20 years. He was admitted 45 minutes after the incident, from a gun-pit which had received a direct hit. He had extensive burns of the face, neck, and arms mainly of the second degree, and areas of first-degree burns on the anterior aspect of the trunk and the shins. He was conscious, with pulse 110, respirations 22, and blood-pressure 120/60. There was haemorrhage into both ear drums. Nothing abnormal was detected on physical examination of the respiratory, cardiovascular, or abdominal systems. In spite of treatment he died 12 hours after admission. A post-mortem examination was made four hours after death. Apart from the burns described above, there was no evidence of external injury. The thoracic and abdominal walls were intact. The pleura contained a few cubic centimetres of straw-coloured fluid. The lungs showed scattered areas of subpleural haemorrhage, not conforming to any pattern. On section of the lungs there were considerable areas of haemorrhage deep in the lung substance, but these did not necessarily communicate with the subpleural areas. The haemorrhagic areas had not the feel of pneumonic consolidation and floated in water. There was slight oedema of the right upper and middle lobes. The trachea and bronchi contained much frothy mucus, which was slightly blood-stained in places. There was no evidence of mediastinal haemorrhage. The bronchial glands were not enlarged. There were no abnormal naked-eye findings in the pericardium or heart. On opening the abdominal cavity the small intestine was found to be grossly distended with gas, intensely congested, and haemorrhagic throughout, with numerous areas of fibrinous exudate measuring about 2 cm. across on the serous coat. No evidence of perforation of the intestines was observed. About 300 c.c. of blood-stained fluid were found in the peritoneal cavity. The vessels of the omentum and mesentery were very congested, and numerous ecchymoses were seen in the mesentery and parietal peritoneum. The mucosal lining of the intestines was congested and small areas of submucosal haemorrhages were seen. The liver showed slight toxic changes. The spleen was firm and not enlarged. The kidneys appeared normal to naked eye examination.

It is difficult to explain the extensive abdominal haemorrhages seen in this case, the ruptured bladder described by Zuckerman, and the ruptured intestines in sailors resulting from the explosion of depth charges on the basis of the distension or suction theories. Moreover, haemorrhages also occur in the muscles and nervous system. We have observed small foci of haemorrhage in the muscles of the trunk; and they appear to afford a possible explanation of the intense muscular pains experienced by some patients with blast injury. Haemorrhages in the brain and spinal cord have been described by Mott (1917) and Zuckerman (1940). We were fortunate in obtaining the brains from four persons found dead in a bunk in a rock shelter without any evidence of external injury and in a group of persons killed in a shelter as the result of blast. Post-mortem examination showed congestion of the vessels of the cerebral cortex with some oedema. In one case there was extensive oedema with flattening of the convolutions of the cerebral cortex. Microscopic examination showed some congestion of the

capillaries with occasional evidence of extravasation of red blood corpuscles in small localized areas, but these latter had no constant distribution. Thus in the brain and cord, as elsewhere, the changes are not specific, consisting of congestion of the vessels and haemorrhage. The intracranial haemorrhages might be accounted for by sudden increase of intracranial venous pressure resulting from the stoppage of the venous return to the heart, but this theory would not explain the presence of haemorrhages in other sites or the rupture of organs. We consider that the nature and distribution of the lesions in human casualties, dying from blast injury, confirm Zuckerman's experimental findings. We also agree with him that it is the traumatic effect of the percussion wave of the explosion upon the body surface which is responsible for the lesions produced in the so-called case of blast injury. Blast is merely a severe and swiftly acting external trauma.

The cause of death in blast injury is unknown. Instances are on record of sudden death immediately after a blow on the abdomen, a blow over the heart, a blow on the head without fracture of the skull, or puncture of the pleura during the induction of artificial pneumothorax. Death in such cases has been attributed to reflex effects upon the vital centres. Similarly in blast injuries, Hadfield has stated that 'it seems more likely that blast produces death by interfering with some vital tissue or centre in which, from the extreme rapidity of action, structural changes are unlikely to be found'.

We are unable to bring forward any new evidence as to the mechanism of death in cases of blast injury. Changes in the functions of vital centres may occur without producing any visible macroscopic or microscopic changes, and as trauma is a known cause of sudden death, we consider that there is no need to assume in the case of blast injuries that any specific mechanism is responsible.

Clinical Findings

The clinical descriptions of blast injury, like the pathological reports, have been mainly confined to the respiratory findings. In the present survey attention has been given to all systems. All casualties admitted to a Military Hospital were examined immediately or within a few hours of admission. A special record was made, after observation of the obvious wounds and injuries, of the condition of the ear drums, the blood-pressure, and the respiratory, cardiovascular, and abdominal systems, even though the patients had no symptoms relating to these systems. Data relating to an incident were obtained from all casualties and as many witnesses as possible. All cases in which there was any suspicion of exposure to blast were studied. The remaining cases were observed more especially from the respiratory aspect in order to provide an adequate control. The classification of blast injuries is difficult, and we shall therefore proceed to describe some of the general findings and illustrative cases.

Ears. Zuckerman (1942) stressed that observation of the ear drums was likely to prove of great value in assessing supposed cases of blast injury. With one exception we found evidence either of congested vessels, or

haemorrhage, or perforation with or without haemorrhage in all cases diagnosed clinically as suffering from blast injury. Fraser and Fraser (1917) described similar injuries to the ear resulting from the proximity of service personnel to the site of loud explosions. Alexander (1941) reviewed war-time injuries to the drumhead, more especially the question of rupture, and mentioned blast as an aetiological factor. Deafness and injury to the ear drum are recognized findings after close exposure to gun-fire (Passe, 1940) and it is difficult to decide in the case of naval and military gunners whether the findings should be attributed to the effects of gun-fire or of blast. Observation of the ear drums of gunners admitted to hospital for complaints other than blast injuries has led us to conclude that some degree of differentiation is possible. Even patients with long standing tears known to be due to exposure to gun-fire show, if later exposed to blast, congestion of the vessels around the malleus. When the ear was full of cerumen, this had been tunnelled through and a small section if not the whole drum was visible. Both ear drums were not by any means affected equally. The slightest degree of change was congestion of the vessels over or in the immediate vicinity of the malleus. Rupture was usually situated centrally or anteriorly. In cases of rupture associated with haemorrhage in an unconscious patient it is necessary to exclude, by means of radiological examination, the possibility of an associated fracture of the base of the skull. In one case (Case 1) with severe haemorrhage and rupture, no fracture of the skull or other gross intracranial abnormality was observed on post-mortem examination, so that we felt justified in considering the ear lesion to be due to blast, as there was evidence of blast injury to the lungs. In addition to the changes in the drum we were impressed by the dilatation of the minute vessels of the aural canal in the quarter of an inch immediately distal to the drum. Most of our patients experienced a period of diminished hearing, varying from a trivial loss lasting an hour or two—the subject experiencing difficulty in hearing ordinary conversation and tending to shout when speaking—to a serious degree of deafness lasting several days or weeks and gradually improving. To crude testing all the minor cases appeared to have recovered normal hearing within 10 to 15 days, but only simple tests were available and a complete follow-up scheme was not attempted. Most patients with extensive bilateral rupture exhibited other serious symptoms and signs of blast injury, and did not survive. Those with rupture of one drum recovered their hearing in the affected ear to a considerable extent, but recovery was by no means complete. All patients with perforation who survived had the affected drum insufflated with sulphanilamide powder and in no case was there evidence of secondary infection.

Blood-pressure. Very few observations of blood-pressure in blast injury have been reported. We found the blood-pressure readings on admission to hospital, usually one to three hours after the incident, to be normal or raised in uncomplicated cases. All readings were taken with a Baumanometer and the recorded result, where possible, was the mean of three readings. The

readings were taken from the arm, with the patient recumbent. The presence of a low blood-pressure, systolic below 100 mm. was not observed unless there was an associated lesion, such as haemorrhage, burns, or extensive wounds, capable of producing a serious degree of surgical shock, or the patient was moribund. Fatal cases of blast injury unaccompanied by other injuries and dying within a few hours of admission, although manifesting clinical evidence of pulmonary congestion and tachycardia, maintained a normal or raised blood-pressure until an hour or so before death. The initial systolic reading—the patients were male subjects aged 19 to 38 years—varied from 100 to 160 mm. The diastolic readings varied from 60 to 88 mm., save in one case where the reading was 100 mm. Considerable difficulty was sometimes experienced in obtaining the diastolic reading. Further, in some cases there was a greater difference than normal between the British and American diastolic end-points. All blood-pressure figures quoted in the present paper refer to the British diastolic end-point.

Respiratory symptoms. The chest has received most attention in reports of blast injury. In patients killed instantly, blood-stained frothy fluid or blood has been described issuing from the mouth and nares (Hadfield, Ross, Swain, and Drury-White, 1940; Wilson and Tunbridge, 1943). Dean, Thomas, and Allison (1940) reported six patients with chest symptoms, first manifested by cough and expectoration between the second and fifth day after the bombing; none complained of pain in the chest and none had blood-stained sputum. Of the 16 patients with physical signs related to the chest, 15 showed fullness of the lower chest, but no tenderness or surgical emphysema. The remaining physical signs were very varied, diminished diaphragmatic movement, diminished air entry, impaired resonance, or added sounds; they were not all found in every case. Hadfield (1941) outlined the main clinical manifestations of pulmonary concussion as being the rapid development of shock, extreme expiratory dyspnoea, frequent thready pulse, restlessness, severe pain, and great tenderness of the trunk. Haemoptysis was common within an hour or so of the incident. Livingstone (1940) reported tachycardia, slight loose cough, occasional blood-stained sputum, and fine crepitations and diminished air entry after 20 hours. Roberts (1940) stressed that serious symptoms did not always develop immediately, but often came on after 48 hours or more.

The varied clinical picture encountered in cases of blast injury or pulmonary concussion is illustrated by the cases reported above and the following cases. Cases 3 and 4 were working close to a heavy gun site when a bomb dropped less than 10 yards away; they were admitted to hospital approximately 90 minutes later. The exact size of the bomb was not known, but was estimated as being 250 kg.

Case 3. A Maltese subject, aged 20 years. He was admitted complaining of pain in the right side of the chest, aggravated by breathing, shortness of breath, and deafness. He was slightly confused. There was no cyanosis, but some fullness of the lower chest and extreme tenderness over the lower right

six ribs. Temperature 98.8° F., pulse 96, respirations 32, and blood-pressure 130/84. Physical examination suggested the presence of a fractured rib or ribs on the right side, but there was no evidence of bruising. Chest expansion was limited, there was an impairment of percussion note on both sides of the chest below the third rib, air entry was diminished at both bases, bronchovesicular in quality at the right base, and occasional râles were heard in both sides of the chest. There was haemorrhage into the right ear drum and congestion of the vessels in the left drum. The patient rapidly developed a cough and on the second day after admission was still restless, complained of severe pain in the chest, and began to bring up blood-stained sputum. Radiographic examination of the chest revealed a fracture of the tenth right rib in the mid-axillary line with little displacement. There was a haziness of both lung fields, most marked in the central zones and towards the base. On the third day he had a temperature of 99.4° F. in the morning, but was otherwise apyrexial. The blood-pressure on the second day was 126/84 and on the tenth day 108/68. The sputum remained blood-stained for six days. All physical signs in the chest had disappeared by the tenth day. The only complaint then was of slight deafness in the right ear. The chest was screened after three weeks convalescence and all haziness had disappeared. There were no symptoms, and the blood-pressure was 108/70 mm.

Case 4. A Maltese subject, aged 21 years. He was admitted to hospital complaining of severe pain over the mid-sternum, tightness of the chest, and cough. He was extremely dyspnoeic, with marked congestion of the face and neck. Temperature 97.6° F., pulse 84, respirations 34, and blood-pressure 144/88. The cough was unproductive, and the respiratory excursion was limited. There was impairment of percussion note over the middle of the left chest anteriorly, over a similar region posteriorly, and also at the right base posteriorly. Air entry was diminished over these areas and crepitations were audible on the left side. There was marked congestion of both ear drums. Blood-stained sputum, not frothy, was expectorated within a few hours, and this continued for 10 days. Radiographic examination revealed no evidence of a fracture of the sternum, but there was a well marked haziness in the central regions of both lung fields, especially on the left side. The pulse-rate rapidly fell to between 60 and 70, the respiratory rate to 20, and there was never any pyrexia. The physical signs remained unchanged for about a week and then gradually disappeared, slight signs on the left side of the chest being obtained when the patient was up and about on the tenth day. The blood-pressure then was 140/86, and after three weeks' convalescence 130/72. The patient had a small abrasion of the right hand and left knee which healed without complication.

Case 5. A British subject, aged 29 years. He was carrying ammunition to a gun-pit when a bomb burst on the other side of the pit; he remembered nothing further, having had what he described as a 'complete blackout'. On the way to hospital he was said to have vomited blood and coughed up blood. He was admitted about two hours after the incident, somewhat dazed, and complained of tightness across the chest and shortness of breath. There was no evidence of bruising or of any external injury. Temperature normal, pulse 74, respirations 26, and blood-pressure 130/80. The chest was emphysematous and there was well marked fullness of the lower thoracic region, but no evidence of surgical emphysema. There was no appreciable change in the percussion note, air entry was poor on both sides of the chest,

and rhonehi were audible. There was slight rigidity of the upper abdominal muscles. The right ear drum was congested, the left drum not visible. The next day he still complained of tightness across the chest and nausea. The cough was unproductive. Two days later he had paroxysms of coughing, but no blood-stained sputum. There was no evidence of melaena, and no nausea or abdominal rigidity. Rhonehi and râles were still audible on both sides of chest. On the third day screening of the chest revealed haziness of both lung fields, particularly the right central and lower lung field. Rescreened after 10 days, the lung fields were normal. No abnormal physical findings. Blood-pressure 130/78.

Case 6. A Maltese subject, aged 38 years. He was in the entrance to a shelter when a bomb dropped within 15 yards. The exact position of the patient and calibre of the bomb were not known. On admission about one hour after the incident the patient was dazed and disinclined to talk (no morphia had been administered). There was no evidence of external injury. Temperature 97° F., pulse 96, respirations 15, and blood-pressure 124/82. On physical examination of the chest the only abnormal finding was the presence of an occasional râle and rhonehus in both lungs. Oxygen was administered and warmth applied. Consciousness returned, a paroxysmal cough developed, the respiratory rate increased in an hour to 26, and the pulse rate fell to 84. On physical examination of the chest there was evidence of dullness on percussion of both bases and diminished air entry, more marked on the left. Eight hours after admission, there was a marked deterioration in the patient's condition. He was orthopnoeic, sleeping fitfully with occasional paroxysmal cough, and the sputum was thick and tenacious, but not blood-stained. Temperature 98.4° F., pulse 116, and respirations 44. Next morning the patient's condition had improved, there was less respiratory distress, temperature 98.8° F., pulse 108, and respirations 36. His condition continued to improve slightly for the next 36 hours, with the cough if anything easier, and no evidence of blood in the sputum. Rhonehi and râles were, however, more evident. The blood-pressure on the second morning was 130/86. On the evening of the third day, 54 hours after admission, the temperature was 103.4° F., pulse 124, and respirations 42, and evidence of consolidation at the base of the left lung was present. The sputum was mucopurulent. A full course of sulphapyridine was begun, 2 gm. at once and 1 gm. four-hourly, and oxygen therapy resumed. There was a general deterioration of the patient's condition, the temperature never fell below 102.8° F., and he died on the fourth day after admission. Permission for a post-mortem examination was refused.

Reviewing the cases we consider Case 1 a typical example of severe blast injury with the lung condition predominating both clinically and pathologically. On admission we thought that he had in addition a fractured base of the skull, but this was not confirmed at autopsy. Case 5 is an example of mild blast injury. In Case 3 had we not been making a special study of blast injury, we should have attributed all the symptoms to the fractured rib. The radiographic findings in both lung fields, however, could not be explained by the fracture of one rib, and the occurrence of haemoptysis, although a recognized finding after fracture of a rib, is extremely infrequent, especially after such a limited injury and one associated with little displacement. Case 4 should be classified as mild to moderate, the chief interest being the

intensity and localization of the pain. This was so marked and local tenderness so pronounced that only careful radiographic examination was able to convince us that the sternum was not fractured. Case 6 raises several interesting possibilities and resembles slightly the case described by Hadfield and Christie (1941). We have not seen many examples of this type, but we consider that the disorder is not entirely one of blast. In severe cases of blast injury death occurs within a few hours or at the latest 48 hours after the incident, the patient's condition remaining critical throughout the period, although he may have phases of slight improvement. We believe that the clinical picture seen in Case 6 results from a secondary infection of the haemorrhagic areas and that the delayed illness, usually manifesting itself 48 to 72 hours after the incident, is a pneumonic or bronchopneumonic process. We suggest that any case of suspected primary blast injury of lungs developing fever of over 100° F. after 48 hours should be given sulphapyridine and treated as a pneumonia.

Abdominal symptoms. In the reports of air raid casualties there have been few references to abdominal symptoms attributable to the effects of blast. There are, however, as already stated, several reports of the effects of depth charge explosions. Abdominal symptoms and signs have been an infrequent feature in our experience. Case 2 had severe symptoms, but initially we attributed the vomiting to the general condition of the patient rather than to a specific abdominal lesion. Burns are often cited as a cause of duodenal ulcer, but we are unfamiliar with any account of burns causing the extensive intestinal lesions observed in Case 2. Case 5 was said by the Unit Medical Officer to have vomited blood and coughed up blood prior to admission; he certainly had abdominal rigidity and nausea, but we were never able to obtain evidence of haemoptysis, haematemesis, or melæna. The following two cases appear to be authentic instances of abdominal injury due to blast.

Case 7. A British subject, aged 26 years. He was proceeding from an ammunition store to the gun site when a bomb dropped approximately 10 yards away. He suddenly felt 'as though someone had hit him in the stomach' and he fell to his knees, he 'blacked-out' for a short interval and the next thing he remembers is being carried to the billet by his comrades. He is quite certain that no object struck him and this view was corroborated by a witness who said that only dust was thrown up by the explosion. On admission two hours after the incident, he complained of headache, fullness in the abdomen, and tightness across the chest. There was a pink congestion of the face and neck, definite fullness of the lower chest, and diminished air entry at both bases, especially on the right side and extending up to the angle of the scapula. There was definite rigidity of the upper right rectus muscle. Temperature 98.2° F., pulse 84, respirations 22, and blood-pressure 130/100. Both ear drums appeared normal. The following day the patient complained of nausea, and he still had abdominal rigidity, but no fever. The pulse rate was 80. He developed suffusion of the left eye. Three days later he first expressed a desire for food, abdominal rigidity was less marked, he was constipated, and an enema was given with normal result. The left eye was then normal. He had an uneventful convalescence and returned to duty

on the ninth day. The chest was screened on the second and the ninth days. On the first occasion there was slight haziness in the right middle and lower lung field, similar to the picture of congestion of the lungs in the early stages of congestive heart failure. This haziness was not observed on the second occasion.

Case 8. A British subject, aged 33 years. A stick of bombs fell close to the gun site, but the number and distance not known. The patient lost consciousness and on admission three hours later, after two haematemeses of at least half a pint which were seen by the Unit Medical Officer, he complained of deafness and of severe pain in the right side of the abdomen and the lower third of the right chest. He avoided movement. On physical examination, the temperature was normal, pulse 104, respirations 28, blood-pressure 132/72, and there was no evidence of bruising or external injury. There was considerable haemorrhage into both ear drums. There were no very definite physical signs in the chest save slightly diminished air entry in the right lower chest, which was attributed to restricted movement. There was marked rigidity of the right side of the abdomen, maximal to the right of the umbilicus and associated with tenderness. Physical examination also revealed impaired vision of the right eye, but the fundi were normal and no other abnormal finding in the nervous system was detected. On the second day there was marked anorexia and nausea; the abdominal rigidity was unaltered, and the pulse-rate never rose above 108. There was no fever. On the third day he was put on small feeds of 3 to 5 oz. of fluid, and vomited twice, but there was no evidence of blood. The bowels were opened, but there was no suggestion of melaena. The abdominal rigidity and pains gradually disappeared without the development of fever or any untoward symptoms, and he was symptom-free and taking a light diet by the ninth day. The leucocyte count on the second day was 6400 per c.mm., 65 per cent. being polymorphonuclear cells. No physical explanation was found for the eye condition, which recovered dramatically on the fifth day. This soldier had an undoubted mild anxiety state on account of air attacks and the eye condition was considered to be hysterical.

The abdominal symptoms in blast injury being of infrequent occurrence are readily overlooked, as in Case 2, where they were at first attributed to surgical shock. The abdominal rigidity in Cases 5 and 7 could well have been due to reflex causes arising as a result of the lung changes. This was the view taken in Case 5, but in Case 7 the persistence of the abdominal rigidity associated with nausea and anorexia led us to conclude that some abdominal injury had been sustained. In Case 8 the degree of abdominal rigidity made us consider the possibility of perforation or rupture of an abdominal organ; in fact a surgical colleague seriously considered surgical intervention.

Nervous symptoms. We have not seen any instances where definite neurological signs could be attributed to blast injury as reported by Stewart, Russel, and Cone (1941), but have observed cases of concussion in which we consider the blast wave to have been the causative agent.

Radiographic findings. Dean, Thomas, and Allison (1940) noted radiological changes in 14 of their reported cases. In 10 the positive findings were diminution of rib expansion with slight loss of translucency, mainly on

the left side. Serial radiographs were not possible in the present study owing to supply difficulties. In consequence we have had to rely upon radiographic screening and an occasional plate for the more serious cases, usually only if there was a suspected associated intrathoracic lesion. The most characteristic finding in the mild and moderate cases was a loss of translucency and congestion in the central and lower portions of the lung fields, similar to that seen in the early stages of congestive heart failure. There has been no predominance of the changes on one side. The findings have been observed on the second day, the earliest day of examination, and in the milder cases had disappeared by the tenth day. In the more severe cases, especially those with delayed symptoms, more varied features have been observed.

Treatment

Minor cases of blast injury call for no special treatment. Rest, warmth, and morphia usually suffice. With battle casualties morphia has usually been administered prior to admission to hospital and its further use is necessary only in cases of extreme restlessness. The very severe cases rapidly pass into a state of semi-consciousness and in consequence rarely require the further administration of sedatives. In the more serious cases, the continuous administration of oxygen, fluid restriction, the use of magnesium sulphate enemata, and venesection are the main therapeutic measures. When there is surgical shock in addition, due to the presence of other injuries, we have been led to the view that the normal methods of combating shock, including the intravenous administration of whole blood or blood products, should not be withheld even though theoretically and practically there is a risk of increasing the pulmonary congestion. The results when surgical injuries or burns are associated with a moderate degree of blast injury and with shock—initial systolic blood-pressure on admission below 100 mm.—have been in our experience disappointing. We are of opinion that in such cases any form of intravenous therapy is usually a waste of valuable stores, the use of which should be reserved for cases with a more favourable prognosis. In cases developing fever of 100° F. or over 48 hours after admission it is advisable to give a course of sulphapyridine as for a case of pneumococcal infection. Patients with abdominal injury are liable to vomit and special care is necessary in their nursing.

Discussion

Evidence has been submitted that the main post-mortem findings in cases of blast injury are congestion of the blood-vessels, more especially of the capillaries and smaller arterioles, and haemorrhage. The lesions occur in any part of the body, but the lungs and ear drums are the sites most commonly affected. The clinical manifestations, like the pathological findings, are in no way specific, can be fully accounted for by the presence of haemorrhages, and are also referable in the main to the respiratory system and the ears. We have shown that a blow is capable of producing identical

lesions, and the more widespread distribution of the changes in blast injuries is due to the intensity and wider spread of the traumatic force in the case of blast.

The symptoms and signs in cases of blast injury may conveniently be classified as of minor, moderate, and severe degrees. The majority of cases exhibit only minor symptoms and signs, and their significance is often overlooked. Incomplete examination or the presence of an associated injury giving rise to more acute symptoms and hence masking the less severe symptoms of blast injury are the main reasons for the minor cases being overlooked. This oversight is not serious for the symptoms and signs in the minor case of blast injury rapidly subside and leave no sequelae. Occasionally, however, when there is no associated surgical injury the unfortunate patient may be considered to be malingering or a case of psychoneurosis.

The patients with moderately severe blast injury constitute a more serious problem and for clinical purposes may be subdivided into three groups.

(a) Those with injuries referable to blast alone.

(b) Those with blast injuries and an associated injury.

(c) Cases of either group (a) or (b), in which the onset of serious symptoms is delayed for 48 hours or more.

This classification is of necessity arbitrary, but it serves to illustrate the clinical character of the problem. The patients with moderately severe blast injuries, without an associated injury, usually exhibit respiratory, abdominal, or nervous symptoms, singly or in combination, from the onset, although these may not become obvious until late in the first 24 hours. In cases with an associated injury this tends to obscure the picture. There may for instance be evidence of shock and in consequence the respiratory or abdominal symptoms may be attributed to the results of the surgical lesion, and the possibility of blast injury overlooked. We stress this group of cases not because we consider that the presence of blast injury should interfere with the normal routine treatment of the surgical lesion, but because both we and our surgical colleagues in Malta have been impressed by the unresponsiveness to therapy of this class of case. Many patients, with what in civil practice would have been considered comparatively minor injuries, suffer from a degree of shock out of all proportion to the blood loss or tissue damage.

The patients with delayed symptoms constitute a problem not merely because these delay convalescence, but because if an anaesthetic has been administered they are often considered to be due to some post-operative chest complication. Fortunately the error is not a serious one, although the cases themselves are difficult to treat. The severe cases in our experience do not constitute a difficult clinical problem, because they are usually seriously ill from the start and the course is progressively downhill. During the first two hours, after recovery from the initial prostration, an inexperienced medical officer may be inclined to overlook the serious nature of the injuries. The presence of haemorrhage in the ear drums, the blood-pressure, the

dyspnoea, and the presence of rhonchi or râles in the chest should be sufficient to warn him that the casualty is not merely 'shocked' in the popular sense of the term, but is one that should be admitted to hospital.

The clinical importance of blast injuries has in our opinion been over-emphasized. Apart from the rapidly fatal cases, and these should be rare provided that adequate precautions are taken during air raids by lying flat on the open ground or in an open slit trench, the only significant feature is the possible deleterious effect exposure to blast may have upon the normal defensive mechanisms of the body.

Summary

1. The main pathological and clinical findings in cases of blast injury are described and discussed.

2. Evidence is submitted to confirm Zuckerman's theory that it is the traumatic effect of the percussion wave of the explosion upon the body surface which is responsible for the production of the lesions.

We desire to express our thanks to Professor Bernard, Director of Public Health in Malta, to the authorities of the Central Civil Hospital, to Professor P. P. Debono, and to our medical and surgical colleagues in Malta for permission to see cases under their care; also to Major Geal, R.A.M.C., for assistance with the post-mortem examinations of certain cases.

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Editorial Note. This paper is an abridged version of a longer report which cannot in the present circumstances be published in full. As the authors are both in distant theatres of war, it has not been possible to submit proofs to them.

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INDUSTRIAL TOXICOLOGY¹

By DONALD HUNTER

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It was not until the nineteenth century, with the rise of industrialism on the one hand and the concomitant development of chemistry and medicine on the other, that our knowledge of industrial poisoning developed. The twentieth-century physician must know something of the dangers which may occur in the chemical, metallurgical, aircraft, munitions, ceramics, textile, cellulose lacquer, and moulded plastics industries. The present rate of industrial development demands the frequent discovery of new materials. The substances produced rapidly become indispensable, but their properties may remain for a long time insufficiently understood. Some of them are dangerous under certain conditions; how dangerous has on several occasions not been realized until a fatal accident has occurred.

It therefore happens that the doctor practising in an industrial area may have to deal with patients exposed to substances which until recent years were little more than chemical curiosities, including aromatic *nitro-* and *amino-*compounds, chlorinated hydrocarbons, ketones, and glycol derivatives, some of which are harmless and others so deadly that their use might with advantage be forbidden. Some are absorbed by inhalation, others through the skin; some attack the liver, causing toxic jaundice, others the kidneys, causing suppression of urine; some affect the blood, causing

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Croonian Lectures for 1942; not delivered owing to the war.

methaemoglobinaemia with lilac cyanosis; others attack the bone marrow, causing thrombocytopenia, leucopenia, and even aplastic anaemia.

To understand how chemical substances exert their toxic effects in industry involves a knowledge of many things. In the case of the metals and their compounds toxicity depends upon physical properties, valency, route of absorption, and upon whether the compound is organic or inorganic. As to the aromatic and aliphatic compounds certain generalizations can be made concerning the relationship of chemical constitution to physiological activity, but there are no inflexible rules. Toxic activity depends not only on chemical constitution, but also on physical properties, especially volatility. As a rule solids are less dangerous to handle than liquids, and a volatile liquid is attended with more danger than a non-volatile one. The danger from solid non-volatile substances is influenced by the fineness of the powder used. The method of handling a given compound is another important factor; of two substances of different toxicity handled in a factory the less toxic may give rise to more poisoning because it has to be transported and handled to a greater extent.

THE METALS

A metal may enter the tissues without acting as a poison. Thus, silver produces no toxic symptoms, but it can lead to life-long disfigurement. In generalized argyria the dust of the metal or its salts becomes precipitated in the tissues in the metallic state and in this form cannot be eliminated. Local argyria arises where small particles of the metal tattoo the skin (Harker and Hunter, 1935).

Of the metallic poisons only lead, arsenic, and mercury will be considered in detail. Their compounds have different effects according to whether they exist in organic or inorganic form, whether their physical properties are those of a solid, a liquid, or a gas, whether the valency of the metal radicle is high or low, or whether they fall upon the skin or enter the body through the respiratory or alimentary tract. Arsenical poisoning occurs in industry in two forms, the first from contact with the dusts of compounds of arsenic, and the second from inhalation of arseniuretted hydrogen. The symptoms in the two groups bear little or no resemblance to one another.

Men poisoned by tetra-ethyl lead show cerebral symptoms and signs, the well-known symptoms of poisoning by inorganic compounds of lead being absent. Similarly, men poisoned by methyl mercury compounds do not show the symptoms and signs of poisoning by the metal itself, but they present symptoms and signs of a unique disease of the nervous system. A third metal showing a specific selection for certain parts of the brain is manganese. This attacks the globus pallidus, the lenticular nucleus, and the caudate nucleus, and the patient shows the corresponding signs of involvement of the extrapyramidal motor system (Charles, 1922).

In the case of chromium compounds toxicity is determined by the valency of the metal radicle. Chromium plating exposes the worker to spray or

mist which is carried into the air by bursting bubbles over the plating vats. Hexavalent chromium compounds are used and they attack the skin through the slightest abrasion, causing dermatitis and the well-known *chrome holes* or *chrome ulcers*. In addition, perforation of the nasal septum occurs in more than half of the men exposed. This toxic action is confined to the compounds of hexavalent chromium. Trivalent chromium salts such as the phosphate and carbonate have no toxic action (Akatsuka and Fairhall, 1934).

The physical form in which a metallic compound exists in the atmosphere may determine its toxicity. Thus zinc oxide may produce toxic effects when inhaled as fume and yet be relatively inert when inhaled as dust. Lead absorption is always greatest among those exposed to freshly formed lead fume. Thus in the occupation of lead burning performed with an oxy-acetylene flame 100 per cent. of men absorb lead, whereas in spray painting only 44 per cent. do so (Fairhall, 1936).

Nickel is not toxic except as the gaseous compound nickel carbonyl. Experimental investigations show that the poisonous effects are entirely due to the nickel of the compound and not to carbon monoxide (Armit, 1907). After the gas has entered the respiratory tract it splits up, depositing nickel as a slightly soluble compound in a fine state of subdivision over the surface of the lungs. This causes congestion and oedema. In man the symptoms come on immediately after inhalation of the gas and consist of giddiness, dyspnoea, nausea, vomiting, cough, and haemoptysis. They all pass off rapidly in the open air. No abnormal physical signs are to be found in the lungs. Although at the time exertion causes distress in breathing and cyanosis, there is no permanent disability and the affected workman is disabled only for a short time. Fatal cases show at necropsy oedema of the lungs and extensive haemorrhages.

Many new alloys which entail the use of unusual metals are being developed. Exposure to fume in cutting copper-beryllium alloys is a source of danger in aircraft construction. Beryllium steel has such remarkably valuable properties that it will doubtless receive much commercial attention. In the preparation of this alloy a certain amount of dust is continually given off by the molten salt electrolytic baths. This dust consists of sodium silico-fluoride, barium fluoride, beryllium oxide, and beryllium fluoride. The dusts of all these compounds are known to be toxic to animals. Other metals, rare or unknown a few years ago, are now assuming commercial importance, especially indium, rhenium, gallium, cerium, and titanium. Whereas little is known as to the toxicity of these substances it can be stated definitely that thallium and cadmium fume are extremely toxic.

Lead. Lead poisoning occurs in industry in two forms, the first from handling the metal and its inorganic compounds, and the second from handling organic compounds, especially tetra-ethyl lead. Lead is now encountered in more than 200 industries. The annual world production of pig lead exceeds 1,500,000 tons, and in Great Britain alone more than 25,000

tons of white lead and 20,000 tons of red lead and litharge are manufactured annually. In 1938, in Great Britain there were more than 1,500 workers in the lead industries and 150,000 painters.

In 1839 Tanquerel des Planches wrote: 'All the characteristic traits of the primary effects of plumbism may be quickly observed in workmen who are habitually in an atmosphere of lead dust and vapour. None of the primary effects are found in workmen who handle lead in a fixed state.' In the intervening hundred years other clinical observers have come to the same conclusion. For example, Legge and Goadby (1912) stated that in industry absorption through the respiratory tract is a 100 times more important than by the gastro-intestinal tract.

Until the work of Arb, Fairhall, Minot, and Reznikoff (1925), observations of a quantitative nature on lead absorption were lacking. These workers realized that the majority of the fundamental physiological problems concerning plumbism were still unsolved, and that the results of previous experiments were for the most part contradictory, inaccurate, or incomplete. Their work has thrown great light on the puzzling problems of lead absorption, storage, and elimination, and on the mechanism of its action on blood, muscle, and nerve. New methods for the detection and quantitative estimation of small amounts of lead in biological material were perfected by Fairhall (1924). The titrimetric chromate method which he devised can be used to an accuracy of 0.1 mg., so that the whole subject was endowed from the start with a degree of quantitative security which it had lacked previously.

Careful studies made by Minot in cats showed how readily absorption occurs from the respiratory tract. She analysed all the organs quantitatively for lead by Fairhall's method, and found that as much lead may be absorbed in one day from a single injection into the respiratory tract as from gastro-intestinal exposure lasting for months. When lead was given by stomach tube in cats most of it could be promptly recovered in the faeces. This occurs partly because most of the ingested lead is not absorbed, and partly because a great proportion of the fraction which is absorbed is taken up by the liver and excreted into the intestinal tract by way of the bile. Very large doses (50 mg. per kilogram three times a week) are required to poison a cat when given orally, and they must be continued for weeks before symptoms of intoxication appear. Thus the experimental method has confirmed the truth of the clinical view that dust and fume should be minimized in order to prevent lead poisoning.

Men are exposed to danger in the smelting of metals, in vitreous enamelling, pottery glazing, shipbuilding, coach painting, plumbing, soldering, and house painting, and in the manufacture of white lead, red lead, litharge, rubber, glass, cement, varnish, coloured pigments, linoleum, and electric accumulators. Lead smelters are exposed to the fume and dust of furnaces and flues. Lead burners and chemical plumbers use oxy-acetylene, oxy-hydrogen, or oxy-coal-gas blow-pipes in their work. The very high temperature of such flames constitutes a much greater risk than that faced by the

domestic plumber who uses a paraffin blow-lamp. There is some risk to compositors who handle typemetal, and to gasfitters who use red and white lead.

It frequently happens that changes in methods or the appearance of new industries provide new causes of lead poisoning. This was the case with ship-breaking following on the scrapping of warships after 1918. In this industry the volatilization of lead from the paint and red lead stopping on the armour plating occurs in the heat of the oxy-acetylene blow-pipe flames used for cutting purposes. Recently mass production methods in the motor-car industry have provided a new lead hazard. A solder of lead and tin is used to strengthen the welds of the steel body-work of motor cars. A final treatment of the body surface, and especially the soldered parts, by a portable grinding disk gives rise to uncontrolled dust containing lead. This may be inhaled not only by the metal finishers engaged on the actual process, but also by others in the vicinity. The great increase in the use of wireless receiving apparatus and motor cars has led to a greater number of cases of lead poisoning in electric accumulator factories.

Sometimes the converse is true, and lead poisoning is found to show a remarkable diminution in a given industry. Thus, the substitution of machine methods for hand labour has abolished the disease among file cutters. The recent fall in the incidence of poisoning in coach painting is due to the development of spray painting of motor cars with leadless cellulose paints.

The past occupations of the patient should be inquired into, for latent lead poisoning is well known to occur. The present occupation is of great importance and the details of the work which he does should be elicited from the patient. Often a man's occupation does not at first sight suggest that he is exposed to compounds of lead. Thus it is elicited only by a leading question that a man describing himself as a fitter may be exposed to dust or fume of lead. The occupation of a cooper becomes dangerous when the barrels on which he works have contained compounds of lead.

Vitreous enamellers working, for example, on baths, sift a powder containing lead silicate on to the bath which has been heated in a furnace. They sometimes use a compressed-air apparatus which forces the enamel through a sieve. In the electric accumulator trade pasters fill the spaces in accumulator plates with a paste containing litharge and red lead. Colour manufacturers grind colours into a fine powder under edge runners with the production of much dust; they frequently use lead chromate and red lead. A slate mason may construct storage tanks by fixing together slabs of slate with materials containing oxides of lead. A bullion refiner may use a process in which he adds lead to refinable silver in a furnace and taps off molten litharge. A rubber compounder adds oxides of lead to crude rubber in preparation for vulcanization. A perambulator maker may be employed painting the body-work of perambulators and then rubbing down the surface with dry sand-paper. An embroidery worker sometimes stencils materials by dabbing on the pattern commercial white lead instead of chalk.

Individual opinion differs widely as to what is necessary for the diagnosis of lead poisoning. Constipation and slight stippling of red cells are insufficient; neither a blue line on the gums nor detection of lead in the urine can be taken as proof of poisoning, for the patient may be insusceptible. Where a worker is exposed to risk, a diagnosis of lead poisoning can be made before the occurrence of a toxic crisis. A falling haemoglobin percentage, with or without a rising punctate basophilia count, raises a suspicion that absorption is passing into poisoning. This suspicion becomes a certainty when these changes are marked or progressive. The diagnosis offers no difficulty in the presence of colic, palsy, anaemia, or encephalopathy.

Intestinal colic is the commonest manifestation of plumbism. It is 10 times as common as lead palsy. An attack of colic is preceded by several days of constipation. The pain is situated around or below the umbilicus. The patient indicates where it is by spreading both hands widely over the abdomen. He becomes cold, pale, and drenched with perspiration, and may bend over or writhe in the bed in intense pain. Examination reveals a scaphoid abdomen, held tensely, but showing no rigidity. Vomiting frequently occurs at the onset of the pain.

The commonest form of lead palsy is the well-known wrist-drop, which begins on the right side in right-handed persons and later becomes bilateral. The palsy first appears in the long extensors of the middle and ring fingers. It spreads to the other fingers, and then to the long extensors of the wrist. The supinator longus and usually the long abductor escape. The brachial type of paralysis involves the deltoid, biceps, and supinator longus, but rarely occurs without wrist-drop. A third form of lead palsy used to occur in the left hand of file cutters who were exposed to the dust and fume of lead. There was progressive atrophy of the thenar and hypothenar eminences and of the interossei. Since fatigue plays an important part in determining the site of lead paralysis, this type of palsy is of great interest, because file cutters not only used the muscles mentioned, but placed a greater strain upon the left hand than upon the right. The substitution of machine methods for hand labour has abolished lead poisoning amongst file makers. Lead palsy rarely occurs in the lower limbs, but when it does it affects the extensors of the toes, giving rise to foot-drop. In the days of prohibition in the United States of America this form of palsy was seen in cabaret dancers who had partaken of alcohol distilled with the aid of a coil of lead pipe.

The paralysis is in the first instance a muscle disease. Fatigue plays an important part in determining the sites attacked. Where the muscle palsy is neglected the lead attacks the motor nerve fibres and ultimately the anterior horn cells of the spinal cord. Paralysis does not appear to be related to the length of exposure. It may develop during the first month of work, or only after many years' exposure.

Experimental evidence supports the clinical view that the lesion begins in muscle. Thus Aub and Reznikoff (1924) devised experiments which showed

that the diffusion of inorganic phosphates from isolated frog's skeletal muscle immersed in Ringer's solution is greatly increased when lead salts are added to the solution. These observations, which indicate that lead may readily alter the chemical relationships in muscle, were followed by others which showed that leaded muscles tire more readily than their normal fellows, and that phosphate diffusion is extremely rapid in fatigued leaded muscles. Lactic acid which forms in muscle cells as the result of activity combines with the lead phosphate in the blood to form lead lactate. As this soluble lactate comes into contact with inorganic phosphate at the surface of the muscle cells the lead is re-precipitated as insoluble phosphate causing alteration in the surface permeability. Efforts to show that reasonable concentrations of lead affect the conductivity of nerve were unsuccessful.

On this basis further experiments were made on intact animals. Cats were exercised in a revolving drum and the fatigue produced was increased locally by attaching a weight to the right fore-paw. It soon became apparent that if the animals were given lead the limb most affected was the one raising the weight. In other words, lead attacked the site of greatest fatigue. The weighted foot showed signs of weakness after about two weeks of exercise. The threshold of the weighted muscle to stimulation through nerve was higher than that of the opposite foot, and a similar difference was apparent with direct muscular stimulation in most of the cases tested.

The well-known blue line on the gums, sometimes called the Burtonian line, was described by Grisolle in 1836 and by Burton in 1840. It consists of fine granules of pigment, arranged in the form of a dark blue stippled line, within the tissues of the gum and about a millimetre from the border of the teeth. It is more marked round infected or dirty teeth, and is occasionally found on the mucosa of the cheek opposite such teeth. Despite the pigment lying within the tissues careful cleansing of the mouth and teeth often causes it to disappear. It is significant of absorption and not of intoxication. Its intensity and size provide a rough guide to the duration and severity of exposure to lead.

Studies of lead anaemia are important not only because of its clinical significance, but also because a clear understanding of the action of lead on the red corpuscle as an isolated cell throws considerable light on the mechanism of its reaction with other body cells. The evidence that lead attacks the bone-marrow and interferes with haemopoiesis is so scanty as to be negligible. Stippled cells are never found in the bone-marrow in lead poisoning, even when they are numerous in the circulating blood. The toxic action of lead occurs peripherally.

The presence of punctate basophilia in the blood is not a specific sign of lead poisoning. It is seen in pernicious anaemia, leukaemia, the anaemias of carcinomatosis, and in pneumonia in infants. However, its occurrence in these conditions is rare and slight as compared with the frequency and intensity of its appearance during plumbism. For this reason stippling of the red cells in the blood has come to be considered as definite evidence

of absorption of lead. It is present in practically all workers exposed to a lead hazard. It is not an indication of the severity of lead poisoning, but it runs parallel to the state of health. If its presence is detected in a sufficiently large number of fields of the microscope, further exposure to lead in the patient concerned should be prevented. Large granules have a greater significance than small ones and denote excessive absorption or mobilization of lead (Lane, 1931). Punctate basophilia counts are of great value in the prophylaxis of plumbism among lead workers and are essential in the hygienic control of lead processes.

Ehrlich believed the stippling to be of cytoplasmic origin, and this view is undoubtedly correct. The basophilic granules are independent of the nuclear substance and have origin in the reticulum. Not only has direct transition between nuclear fragments and stippling never been observed, but the granules are frequently seen in erythroblasts with intact nuclei. The granules show none of the photographic or staining properties of nuclear substance. There is much evidence of the close alliance of basophil punctation with polychromatophilia and reticulation. The same fixatives and the same differential stains are effective for all three conditions. Blood films can be prepared showing all stages between polychromatophilia, stippled fragments, and typical reticulum. This action of lead on the reticulated red cell is analogous to its effect on other young tissues, such as the chorion epithelium, and the sarcoma cell. Circulating lead singles out the youngest tissues for its attack, and in the case of peripheral blood the youngest cells are the reticulocytes.

Aub and Reznikoff (1924) devised a number of experiments by which they demonstrated the action of lead salts on the cells of the blood. Many of the effects were obtained on washed human red cells exposed to a concentration of only two parts of lead chloride per million (1 c.c. of corpuscles per 0.001 mg. of lead). The surface of the cell becomes hard, brittle, and inelastic; it shrinks, loses its power of agglutination, and shows increased resistance to osmotic surroundings. The interior of the cell is not affected, and so the physiological properties of the haemoglobin remain normal. When the leaded cells circulate in the body, with the trauma attendant on passage through the capillaries, they break up rapidly in the peripheral circulation and anaemia results. The chemical reactions causing these physical changes are the precipitation of insoluble lead phosphate in the cell envelope, with liberation of acid. Because of the loss of circulating red cells, there is compensatory regeneration of the erythrocytes with a high reticulocyte count. The secondary anaemia is mild, and it is rare to find less than 3,000,000 red cells per c.mm.

Encephalopathy is the most dramatic manifestation of lead poisoning and is always of serious prognostic significance. The acute form begins suddenly with epileptiform convulsions. Grisolle (1836) studied 29 such cases and divided them into three groups—convulsive, comatose, and delirious. The convulsive crises seem to be due to toxic meningo-encephalopathy and not

to hypertension, for lumbar puncture shows that though the cerebrospinal fluid is under increased pressure it contains an excess of cells, usually 100 small lymphocytes per c.mm. (Mosny and Malloizel, 1907). Furthermore, in one case of lead encephalopathy 0.08 mg. of lead was recovered from 80 c.c. of cerebrospinal fluid (Aub, Fairhall, Minot, and Reznikoff, 1925). Chronic cases may show mental dullness, inability to concentrate, poor memory, headache, head retraction, trembling, deafness, transitory aphasia and hemianopia, and amaurosis without fundus changes. Writers of long ago described cases of blindness from optic atrophy, but it is not clear whether this was primary or secondary (Hutchinson, 1873). More recently, papilloedema measuring up to six dioptres has been described. Since this is found associated with either unilateral or bilateral paresis of the external rectus oculi it is evidently due to increased intracranial tension (Gibson, 1922). The frequent occurrence of convulsions in lead poisoning is recorded by ancient writers, but with the improvement of industrial conditions the incidence of lead encephalopathy has progressively decreased, and to-day cases are rarely seen.

Transitory pains in muscles and joints are commonly associated with plumbism, and temporary effusions of fluid into bursae and tendon sheaths may occur. In 1854 Garrod pointed out that gout was common among lead workers in Great Britain, but there is nothing to show that the occurrence of these two conditions in one patient is other than fortuitous. Abortion was common among women who worked in the potteries in the days before protective measures were in operation.

Conflicting statements have been made as to whether or not prolonged absorption of lead causes hypertension or Bright's disease. The exposure to lead of young children in the tropical parts of Australia provides suggestive evidence. In Queensland, the paint on exposed surfaces powders producing abundance of lead carbonate which rubs off fences and verandah railings like chalk. Numbers of children living in these houses develop lead palsy in childhood and die at an early age from chronic nephritis; sometimes several members of one family are affected. Nye (1933) studied a series of 34 patients with nephritis who had suffered from lead palsy in childhood. Inquiry showed that they had all spent their childhood in wooden houses; 30 were nail-biters or thumb suckers, all but seven had albuminuria, and 29 had well-established renal insufficiency. Some had renal dwarfism, hypertension, marked urica retention, and low urinary concentration. The death rate was correspondingly high.

Vigdor-tehik (1935) found an association between lead absorption and hypertension, but he based this on single observations of the blood-pressure of 2,769 workers in whom only the systolic pressure was recorded. He gave no serial figures of individual cases and he omitted to state the amount of lead absorption in each worker. Belknap (1936) reported 2,600 serial blood-pressure readings made month by month for over a year in workers who had absorbed large amounts of lead. Of 81 men observed all were heavily

exposed either to fume of molten lead or to dusts of lead oxides, and all showed either a blue line on the gums, punctate basophilia, or high lead excretion in the urine. Fifty-eight per cent. of them had been exposed for periods varying from five to nine years. The cases were studied by age groups. The writer concluded that there was no variation from normal in the blood-pressure. Teleky (1937) disputed the validity of these results on the grounds that the men had not worked long enough in the lead industries to develop high blood-pressure. He stated that he would have expected, from his experience, only sporadic cases of high blood-pressure in men exposed for such relatively short periods.

Fouts and Page (1942) failed to produce hypertension in dogs treated with lead for a long time. One animal received large amounts of lead for three years, a third of its life span. Dreessen (1943) showed that among 776 workmen albuminuria and symptoms of early plumbism were most common in those exposed to the highest atmospheric lead concentration, but the prevalence of arterial hypertension among these employees was not significantly different from that observed in other industrial workers. The figures of the Registrar General for 1931 show there were then 178,170 paperhangers and painters in Great Britain and that deaths from cerebral vascular lesions numbered 398, arteriosclerosis 40, and Bright's disease 265. The standard mortality for the same diseases was 263, 33, and 202. There seems little evidence, therefore, that lead significantly predisposes to hypertension or Bright's disease, except perhaps in children.

In diagnosis there is a danger of wrongly attributing to lead poisoning any symptoms which may occur in persons exposed to lead. Acute appendicitis, chronic gastric or duodenal ulcer, and carcinoma of the stomach occur in lead workers just as they do in others. They must be carefully differentiated from colic. A lead worker can suffer from pernicious anaemia or secondary anaemia due to piles, melaena, or haematemesis. It is important to remember that lead poisoning has to be severe before the red-cell count drops below 3,000,000 per c.mm. In industrial cases the blue line is unlikely to give rise to confusion. A similar phenomenon is commonly seen in patients under treatment with bismuth preparations given intramuscularly. The differential diagnosis of lead palsy should give rise to no difficulty, since the changes are entirely motor. Litigation hysteria is all too common in the lead worker. The manifestations include hysterical spasm of the hand and arm, weakness of various movements, including the flexors of the wrists and fingers, glove and stocking anaesthesia, complete hemi-anaesthesia, and hysterical aphonia. Such symptoms are rarely alleviated until legal proceedings are completed.

The problem of the physicochemical behaviour of lead in the animal body has been approached experimentally. Fairhall (1924) determined the solubility of various lead compounds in serum, studied the reactions and equilibria involved in the formation of the phosphates of lead, and carried out electrometric measurements in which lead salts were added to serum.

His experiments suggest that lead is transported in the blood-plasma as the insoluble tertiary phosphate in the highly dispersed or colloidal form.

Since lead is a cumulative poison there must be some place in the body where it can be retained in fairly large quantities. The work of Gusserow in 1861, followed by that of Heubel in 1871, suggested that this storehouse was the skeleton. Minot and Aub (1924) using Fairhall's method of analysis showed quantitatively that in animals and man nearly all the lead is stored in the bones. Fairhall studied such bones, and the results of his experiments suggest that the lead is present as the very insoluble tertiary phosphate. Various experiments showed that it is deposited in the calcareous portion of the bone and not in the marrow. Minot obtained proof of this by producing lead poisoning in chickens, and examining the respiratory bone of the wings, which consists of a shaft without marrow. She showed that these bones contained relatively as much lead as did the other bones of the chicken. The lead must therefore have been stored in bone and not marrow. In 1932, Aub, Robb, and Rossmeisl showed that lead is stored in higher concentration in the trabeculae than in the corticis of bone.

During different stages of intoxication the distribution of lead within the body varies. When absorption is slow during the chronic stage of plumbism about 95 per cent. is held harmlessly in the skeleton. On the other hand, if lead is being absorbed in large quantity it is distributed more evenly throughout the tissues. Under these conditions acute symptoms of poisoning occur. Analysis of bone obtained at necropsy from lead workers has shown that the total amount of lead stored in the skeleton varies from 0.2 to 0.8 gm.

Since calcium and lead are stored in the skeleton in the form of phosphate the discovery that the excretion of these two substances runs parallel is of great interest. Repeated observations have shown that conditions which favour storage of calcium in the body also favour storage of lead. When conditions are unfavourable for the retention of calcium the excretion of stored lead increases.

In studies of lead excretion it is to be noted that no satisfactory figures can be obtained unless specimens of stools and urine are collected for at least three days. Normal persons with no occupational exposure to lead may excrete lead in the faeces and urine. This happens because lead is frequently present in the soil and hence in vegetation and animal food. Cholak and Bambaeh (1943) found that in 1,052 normal persons with no occupational lead hazard, the mean lead concentrations were 0.030 mg. per 100 gm. of blood, 0.027 mg. per litre of urine, and 0.28 mg. per 24 hours' sample of faeces. Exposure to lead in industry raises these values, and the corresponding figures for 86 men engaged in making white lead were 0.086, 0.241, and 3.76. It is doubtful whether renal excretion exceeds 0.3 mg. in any circumstances.

A man working in a dusty lead industry, in addition to inhaling lead, may swallow repeated small amounts and pass lead unabsorbed in the faeces.

Therefore, to prove the absorption of lead, it is necessary to find excess in the blood or urine. Lead has been found in the stools of persons who have been removed from exposure for more than two years, and Oliver (1914) found it in the urine of a woman 11 years after exposure. Thus, as suggested by Straub (1911) and Erlenmeyer (1913), there may be an intermittent stream of lead entering the circulation which is only gradually excreted.

The conditions favouring liberation of lead from the bones have been studied experimentally in cats poisoned with lead. During starvation acute symptoms may develop suggesting that there is something unusual in the metabolism of the body which sets lead free from the bones. Acidosis seems the most probable explanation for the change (Aub, Fairhall, Minot, and Reznikoff, 1925). Acidosis has been produced in men exposed for long periods in lead industries. They were given either hydrochloric acid, phosphoric acid, or ammonium chloride, in combination with a known low calcium diet containing no milk, eggs, green vegetables, or fruit. Under this regime the excretion of lead in the faeces rose to about 2 mg. in each 24 hours. Fairhall (1924) showed that the tertiary phosphate of lead has an extremely low solubility at the normal pH of the body, but under slightly more acid conditions it is converted into the secondary phosphate which is 100 times more soluble. Hence the ingestion of acid serves to liberate lead from the skeletal stores by converting it into a more soluble salt.

When, in 1925, Collip prepared parathyroid extract it was possible to confirm the hypothesis that the metabolism of lead runs parallel to that of calcium. He showed that the extract, administered to parathyroidectomized dogs, prevented tetany by restoring the level of the serum-calcium to normal, and that elevations in that level could be produced in normal dogs. In 1926 Hunter and Aub studied the effect of repeated injections in six patients with chronic lead poisoning. They were given a diet of known calcium content, routine daily estimations of the serum-calcium were made, and all the faeces and urine were collected for the quantitative estimation of lead and calcium. These analyses showed increased excretion of calcium and lead from the bones; the extract caused elevation in the serum-calcium, an effect observed even on a diet deficient in calcium. When parathyroid extract was first given it greatly increased the excretion of lead from trabecular bone. However, if it were given a second time after an interval it failed to mobilize the remaining lead stored in a less available form in cortical bone. This action confirms the striking parallelism between the storage and excretion of calcium and of lead. No ill effects were produced, but it is a drastic procedure and has little value in practical therapeutics. It might produce acute episodes of lead poisoning or the symptoms of prolonged hypercalcaemia.

In Great Britain preventive measures are carried out with such success that the majority of cases of lead poisoning are mild. It is unusual to-day to meet with a case either of severe colic or of extensive palsy. In industry less than 100 cases of lead poisoning were notified in 1938 as compared with

more than 1,250 in 1899. The most important single measure of prophylaxis is the prevention of dust and fume. As advocated by Legge (1934), success has been achieved by the institution of protective measures over which the worker concerned can exercise no control. One such method is exhaust ventilation applied through hoods at the source of origin of dust or fume. The hygiene of the workshop and cleanliness of the worker are both important. Benches, tools, floors, and walls must be spotless, often at the expense of the constant vigilance of several good foremen. No scrap lead or dry white lead should be handled unless it has been thoroughly soaked by the use of a hose. Mechanical means, such as cranes, rails, hoists, covered conveyors and hoppers, and automatic packing machinery should be substituted for hand carriage.

Since 1899 the lead manufacturers in Great Britain have spent over £200,000 on alterations and dust-removal plant in order to render the conditions of employment more healthy. Fortunately, about 50 per cent. of the white lead manufactured is not handled in the dry state. It is made by the stack process and leaves the stack as an aqueous paste, to be mixed with linseed oil, and made into an oil paste in closed automatic machines without dry grinding. Since a worker in a factory making white lead may handle in the course of a day at least as much white lead as a painter handles in a year the value of this wet pulping method will be realized. In the manufacture of litharge and red lead it is impracticable to use wet methods, and it is therefore necessary to use machinery designed to minimize dust.

In the potteries removal of dust by locally applied exhaust ventilation has accomplished much in the diminution of poisoning. So also has the use of low solubility glaze or frit, a substance introduced by Thorpe (1901). It is a product in which oxides of lead have been fused with the raw constituents of the glaze, thus converting them into the insoluble lead bi-silicate. Up to 1900 red lead or white lead had been almost universally used for pottery glazing, and the good effect of using a non-dusty, highly insoluble substitute can readily be imagined.

Since 1927 it has been illegal for a painter to rub down by dry methods any indoor structure previously treated with lead paint. Dust can be avoided by using a damp rubbing down process for lead painted surfaces. Waxed sandpaper which the workman dips repeatedly in a bucket of water has made this possible (Klein, 1923). At the present time a painter in mixing paint is rarely exposed to dry white lead since it comes to him already mixed in oil.

Paint technologists have invented a non-setting red lead, which is now issued to the painter of metals already mixed in oil. He is therefore protected from exposure to the dust of red lead for he no longer mixes the materials himself. The use of plastic rubber, that is rubber in which litharge has been incorporated in a mother batch to the extent of 90 per cent., has abolished the production of lead dust in certain processes in the rubber industry (Klein, 1922).

In addition to cleanliness in the workplaces, personal cleanliness is of the first importance. Cloak-rooms, washing-rooms, mess-rooms, baths, nail-brushes, towels, and soap must be provided. The hands should always be washed before eating, and the work-people urged to take a warm bath frequently. Food and drink must not be brought into the work-rooms and smoking at work must not be allowed. Medical examination of the workers exposed must be carried out periodically. At present we have no biological test by which to select workmen who are immune to the toxic effects of lead. Since they have been found unduly susceptible, it is necessary to forbid the employment in the potteries and other lead trades of pregnant women and of all persons under 18 years of age.

In the prevention of lead poisoning a diet of high calcium content plays its part. In lead works in Great Britain it has for many years been customary to provide the workmen free of cost with a glass of milk each morning. This is empirical treatment of considerable merit, anticipating as it did by many years the discovery that a high calcium intake assists the storage of lead in a harmless form in the bones. Workers should drink plenty of water which will help to avert constipation and often render the use of aperients unnecessary. Any worker who develops one of the toxic effects of lead has thereby proved his susceptibility, and ideally he should never again work in any department of a lead works.

Curative treatment of lead poisoning is based upon the observation that a high calcium diet causes lead excretion rapidly to diminish. A diet containing four pints of milk a day or a daily dose of 15 gm. of calcium lactate is all that is necessary to store lead in the bones so that it will not be free in the circulation to cause harm.

In cases of lead poisoning showing toxic symptoms the diet should contain three pints of milk daily, and include milk puddings, junket, and ice cream, together with butter, cheese, and eggs. In the presence of acute symptoms no attempt should be made to increase the elimination of lead; so much is already circulating that it is safer to encourage further storage. The first step should be to prescribe large quantities of calcium lactate, 5 gm. (75 gr.) three times a day. When the calcium intake is sufficient most of the lead is stored in the bones, and the patient loses his symptoms.

Colic should be treated by the local application of heat, pressure, and moisture. It is desirable that the bowels should be moved as early as possible by means of enemata of olive oil and warm water, and by the internal administration of magnesium sulphate along with belladonna and carminatives. In his study of untreated lead colic, Tanquerel des Planches (1839) found that it may persist for four to 12 days or more. Bronardel (1904) stated that colic usually yields to treatment within eight days, but that if neglected it may continue for two, five, or even six weeks. Treatment with a high calcium diet almost invariably brings relief within two days (Aub, Fairhall, Minot, and Reznikoff, 1925).

The relief of lead colic by calcium therapy involves more than the ability

of calcium to favour storage of lead. Since the pain is due to violent peristalsis behind a contracted tonic ring of intestine, the anti-spasmodic effect of calcium salts on involuntary muscle is beneficial. In severe cases it is possible, by the slow intravenous injection of 15 c.c. of a 20 per cent. solution of calcium gluconate, or of 10 c.c. of a 5 per cent. solution of calcium chloride, to relieve the pain by the time the injection is over. The patient feels hot and flushed and may vomit. The effect upon the pain is striking and is far superior to that of any other treatment. If necessary, the injection may be repeated in two hours. Should such treatment not be available, a hypodermic injection of atropine sulphate gr. 1/60 may be given.

During the development of lead palsy a high calcium diet should be used to favour the storage of lead. Massage, electrical treatment, and strychnine are also useful. In the early stages the hands, when affected by wrist-drop, should be supported on splints. The paralysed muscles may be stimulated by an induction coil, with or without a water bath, but over-stimulation should be avoided since it induces fatigue and so does harm.

Lead encephalopathy should be treated by lumbar puncture. In the few cases dealt with in the United States of America good results have followed the use of a high calcium diet. Of six cases, three occurred before the treatment was in use and all of these died. The other three were given large quantities of milk and calcium lactate and promptly recovered (Aub, Fairhall, Minot, and Reznikoff, 1925). As a result of regulations for the control of dust and fume the condition is now so rarely seen in Great Britain that the effectiveness of this treatment cannot be accurately gauged.

A few weeks after the acute toxic episodes have passed the elimination of lead may be accelerated by the use of a low calcium diet, together with potassium iodide, ammonium chloride, or phosphoric acid to facilitate the release of lead from the bones. All milk, milk products, green vegetables, and eggs are omitted from the diet which may, however, contain meat, liver, chicken, potato, peas, rice, tomato, banana, apple, lemon, tea, coffee, sugar, honey, salt, and pepper. All bread should be prepared without milk. It is better to substitute butter fat for butter. This is prepared by melting butter in hot water and skimming off the butter fat. In those places where the water supply is hard, vegetables should be cooked in distilled water and all drinks made up with it.

Potassium iodide was first used in the treatment of lead poisoning by Guillot and Melsens in 1844, and has been employed by clinicians ever since. That it is a useful agent for increasing the excretion of lead has been shown by quantitative experiments. It is not as effective as treatment by acidosis, but has the advantage of ease of administration. The dose should be increased from 5 gr. three times a day to 15 gr. three times a day. Its physiological effectiveness appears to diminish progressively after the first few days of treatment. It has been known to precipitate an acute attack of lead poisoning in an apparently healthy subject as long as 16 years after exposure to lead has ceased. Oliver (1914) quoted such a case in which

administration of potassium iodide was promptly followed by the appearance of a blue line on the gums and wrist-drop, although previously there had been no evidence of lead intoxication. The condition has been referred to as *latent lead poisoning*.

Acidosis may be produced by the use of phosphoric acid, but it is more satisfactory to use large doses of ammonium chloride. Chronic lead poisoning may be treated by the cautious administration of this substance in doses of 1 gm. (15 gr.) given in a glass of water eight or 10 times daily for three weeks at a time. The dose should be reduced if loss of appetite and headache appear, for these symptoms indicate the limit of tolerance to such treatment.

Since it would doubtless require several years, it is useless to attempt the elimination of all the lead stored in the body. It is desirable to eliminate only the most readily mobilized lead. In prolonged observations the results indicate that after a certain point elimination of lead becomes progressively more difficult. When this stage is reached it is more practicable to favour its retention in the bones by maintaining a positive calcium balance. Thus, after three weeks' treatment by a low calcium diet and ammonium chloride, there should be a rest period of a week with normal diet and abundance of milk to correct the calcium deficiency. Treatment to accelerate elimination should then begin again. Neither ammonium chloride nor potassium iodide should be used in the presence of nephritis or of toxic symptoms. Should any toxic episode appear during the use of ammonium chloride or potassium iodide, these drugs must be stopped and a high calcium diet at once used to favour the storage of lead.

It is necessary to emphasize the difference between the use of agents which assist excretion of lead and those which assist its storage. The acidosis method of lead elimination is so potent that its use during colic or any other toxic episode might prove fatal from the further mobilization of lead. It is scarcely necessary to add that such treatment should never be used as an excuse for negligence in enforcing all the known measures for the prevention of exposure and absorption.

Tetra-ethyl lead. Tetra-ethyl lead is an organic lipoid-soluble compound readily absorbed through the skin and respiratory tract. It is a clear, heavy, oily liquid with a peculiar sweetish odour, and is somewhat volatile at ordinary temperatures. It is added to petrol in proportions up to 1 in 1260 as an antidetonant (Kehoe, 1925).

In 1923, when it was first manufactured in the United States of America, 149 cases of encephalopathy occurred in men employed on three separate plants. Within 17 months 11 deaths were reported. Much excitement and alarm were caused and this led at first to the prohibition of the manufacture. The men affected suffered from restlessness, talkativeness, ataxia, insomnia, and delusions. There were no paralyses or convulsions, but the condition terminated with violent mania, the patient shouting, leaping from bed, and smashing furniture.

In the most severe cases the mental manifestations dominate the clinical picture, hallucinations and delusions being common. Several symptom complexes have been distinguished—the delirious, manic, confused, and schizophrenic (Machle, 1935). Less severe cases begin with insomnia, sleep being difficult, broken, and restless, sometimes with wild and terrifying dreams. By day, mental excitement may be marked, headache is usual and often severe, and vertigo is frequent. Difficulty of vision owing to weakness of the extrinsic muscles of the eye is an occasional complaint. Evidences of meningeal irritation are absent; the cerebrospinal fluid may at times be under increased pressure, but it is not otherwise abnormal. Anorexia, nausea, and vomiting are constant. Diarrhoea sometimes occurs, and many patients complain of a metallic taste in the mouth. Weakness, tremor, muscular pains, and ease of fatigue are frequent complaints. The tremors affect the extremities, lips, and tongue, and are coarse and jerky, and aggravated both by effort and by attempts at control. In the patients who recover, all symptoms disappear in from six to 10 weeks.

By meticulous attention to detail, it is possible to manufacture tetra-ethyl lead and to blend it with petrol without risk to the workers. Both manufacture and blending are carried out in closed systems. Elaborate precautions are taken in transport, storage, and handling of the fluid, and great care is exercised to avoid leakage or spilling. In blending and laboratory work impervious gloves and respirators are used. Although ethyl-petrol contains less than one part in a thousand of tetra-ethyl lead it should not be used for cleansing the skin and to prevent this it is coloured by a dye. There is little need for apprehension as to the possibility of the poisoning of garage and aircraft workers by lead from the exhaust gases of petrol engines.

Arsenic. Arsenical poisoning occurs in industry in two forms, the first from inhalation of or contact with the dusts of compounds of arsenic, and the second from inhalation of arseniuretted hydrogen gas. The symptoms in the two groups bear little or no resemblance to one another. The compounds of arsenic act as local irritants to the skin and mucous membranes. Only rarely is the dose of arsenic large enough to produce the gastro-enteritis so common when it is administered for criminal purposes. Arseniuretted hydrogen, on the other hand, acts as a powerful haemolytic agent, causing haemoglobinuria, anaemia, and haemolytic icterus.

Arsenical compounds are met with in the smelting and refining of ores, in the subliming of white arsenic, and in the manufacture of sheep dip (sodium arsenite), Paris green (copper aceto-arsenite), and Scheele's green (cupric arsenite). White arsenic is used as a preservative of hides, skins, and furs, and Paris green as an insecticide for fruit trees. The dusts of the arsenical compounds manufactured in industry are light, so that, unless the processes of sifting and packing are carried out in closed apparatus from start to finish, the dust is likely to alight on the skin and remain there.

The skin is affected especially where there are folds, as around the nose

and mouth, or where surfaces are moist, as in the axillae or on the scrotum. Here a dermatitis is set up which, if untreated, leads to extensive ulceration. Associated with the skin eruption are conjunctivitis with oedema of the eyelids, coryza, dryness of the throat, and hoarseness. In severe cases vomiting occurs, but colic is rare. Headache and paraesthesiae in the limbs may occur, but widespread polyneuritis is rare and motor paralysis is practically never seen. Mottled brown pigmentation of the skin, usually on the temples, eyelids, and neck, is present in those who have worked for years in contact with arsenical dusts. In severe cases there may be intense bronzing of the chest, abdomen, and back. The most characteristic lesion produced in the upper air-passages is perforation of the nasal septum, which may be complete in a month from the time of starting work. Once the perforation is complete no further symptoms occur and the worker may be unaware of the existence of the condition.

The widespread use of arsenic and its compounds in industry has led to a prevalent belief that it is responsible for industrial cancer in many occupations. All the available evidence is contrary to such a view, and, apart from that occasionally following long-continued therapeutic administration, skin cancer due to arsenic is rare.

In 1820 Paris described arsenical cancer of the scrotum in tin smelters, but his statement that animals may also be affected has never been substantiated. 'It may, however, be interesting and useful', he wrote, 'to record an account of the pernicious influence of arsenical fumes upon organized beings, as I have been enabled to ascertain in the copper smelting works of Cornwall and Wales; this influence is very apparent in the condition both of the animals and vegetables in the vicinity; horses and cows commonly lose their hoofs, and the latter are often to be seen in the neighbouring pastures crawling on their knees and not infrequently suffering from a cancerous infection in their rumps. . . . It deserves notice that the smelters are occasionally affected with a cancerous disease in the scrotum similar to that which infests chimney-sweepers.'

Hutchinson (1888) first drew attention to the carcinogenic properties of arsenic. He described cases of carcinoma of the skin in patients treated with arsenical mixtures for psoriasis and other skin conditions. A similar effect has since been found in factories where arsenic is handled. The fine powder of arsenical compounds which settles on the skin of the industrial worker may give rise to warts on the nostrils, eyelids, lips, ears, and wrinkles of the neck, and, since these compounds of arsenic are carcinogenic, the warts may become malignant. Cases of cancer of the skin due to occupational exposure to arsenic are seen in hospitals from time to time, but they are rare. In 30 years only three have been seen at the London Hospital, two in 1910 and one in 1924 (O'Donovan, 1928). Each of these patients had been employed for 20 years or more in the sheep-dip industry and each developed a squamous-celled carcinoma. The clinical picture of all was made up of pigmentation, keratosis, and single or multiple malignant growths.

There were no special sites. Face, abdomen, scrotum, buttocks, clavicle, and lower chest were affected. It is suspected that prolonged inhalation of the dust of arsenical compounds causes cancer of the lung. The total number of workers in Great Britain exposed in this way is small and deaths have usually gone unchecked by necropsy. Extensive statistical inquiry, supported by histological proof of the diagnosis, will be necessary before the question can be settled.

In the prevention of arsenical poisoning in industry dust must be suppressed. The floors of workrooms and passage-ways should be of impermeable material, and they should be frequently flushed with water. Workrooms should be well ventilated, and hoods connected with a good draught placed over apparatus emitting dust. All poisonous fume should be condensed and any dust caught removed. Hot processes should be carried out under glass hoods and manipulation of powders in closed glass cabinets. When possible, mechanical methods should take the place of hand labour. Apparatus and receptacles must be strong to avoid breakage. In all processes in which arsenical dust is likely to arise tables should be provided with downward exhaust ventilation. Since the dust of Scheele's green is light it is difficult to protect the workers. Automatic packing is not possible, and the ordinary means of protection by respirators favours sweating and consequent ulceration of the skin. Persons with a moist skin and those who sweat readily are unsuitable for the work and should be excluded. Special working clothes and head-gear, washing accommodation, and towels should be provided. Neither food nor drink should be taken in the work-room, and smoking and the taking of snuff should be prohibited (Balthazard, 1930).

Arseniuretted hydrogen. Arseniuretted hydrogen, known also as hydrogen arsenide and arsine, was discovered in 1775 by Scheele. Its toxicity remained unknown until 1815 when Gehlen, a Munich chemist, in the course of some researches 'inspired a small portion, and at the termination of one hour was seized with continued vomiting, shivering, and weakness which increased until the ninth day, when he died'. Unfortunately, this tragic accident is repeated from time to time.

In 1920 Schierbeck, of Copenhagen, died from arseniuretted hydrogen poisoning during studies made in collaboration with Lundsgaard on the mixture of air in the lungs with hydrogen. Usually the hydrogen was prepared from hydrochloric acid and zinc which were both free from arsenic. As a further precaution the gas was washed by passing it through potassium permanganate solution and a sample was tested for arsenic by Marsh's method (Lundsgaard and Schierbeck, 1923). Towards the end of the experiment the workers ran short of arsenic-free hydrochloric acid, and Schierbeck was imprudent enough not only to make use of ordinary laboratory hydrochloric acid in the preparation of the hydrogen, but also to neglect to wash the gas and to test a sample for arsenic. The evening on which the experiments were made he had fever, diarrhoea, and copper-coloured jaundice. The urine was red-brown and contained albumin and haemoglobin. The

jaundice persisted and within a few days vomiting occurred, the liver became palpable, and the haemoglobin fell from 46 to 31 per cent. His general condition became rapidly worse, dyspnoea was noticed, suppression of urine supervened, and he died on the ninth day after the accident.

The first cases to be reported in industry occurred in 1873 in Germany, in men engaged in recovering silver from lead and zinc ores. In a monograph on the subject published in 1908, Glaister, of Glasgow, summarized all the 120 cases which had been reported up to that time. His work remains the best general account of the subject in English. Since 1908 the number of cases recorded has been more than doubled. The majority of cases have been due to the use of acids and alloys or ores contaminated with arsenic. The occupations concerned are the roasting and extraction of mineral ores, pickling and galvanizing of metals, cleaning of acid tanks, the manufacture of bleaching powder and zinc chloride, the manufacture of hydrogen and its use in ballooning, and lastly the making, charging, and using of accumulators. It follows that the workman may absorb the poison in operations in which the possibility of poisoning is not so much as imagined.

The possibility that poisoning might arise from the action of water on the arsenides of alkali metals was recognized by Jones (1907) and Glaister (1908). In 1923 Legge reported two cases of arseniuretted hydrogen poisoning (one of them fatal) from a dross-refining factory in England. A thunderstorm flooded a floor on which bags containing residues from certain refining operations were stored. Two men were employed packing dross at a distance of 10 feet from these bags. One was quite unaffected, but the other suffered from vomiting, intense coppery jaundice, and suppression of urine, and died. A third man in charge of a drossing furnace some 20 feet away was slightly affected. A sample of a fresh portion of the contents of the bags was found to contain 1.6 per cent. of arsenic, together with lead, tin, antimony, copper, and aluminium. It smelt of sulphuretted hydrogen and when moistened gave off large quantities of arseniuretted hydrogen. In 1932 Bridge gave an account of six cases with two fatalities caused by the damping down to lay the dust of a residue containing a metallic arsenide. He also mentioned three cases which occurred at the same factory earlier in the year and were not reported. In one of the fatal cases traces of arsenic were found in the bones. In 1931 Löning reported 11 cases (with four deaths) which occurred in a tin-refining works at Wilhelmsberg. The patients had been engaged in the process of tin-refining described above and had sprinkled water over the dross to avoid the raising of dust. In 1932 Bomford and Hunter described two cases occurring in London from a similar cause. In the process of tin-refining a dross containing aluminium arsenide was watered down with several canfuls of water while still hot. Two workmen were affected, and both suffered from haemoglobinuria and haemolytic jaundice with anaemia. Both recovered completely. Twenty-five cases of arseniuretted hydrogen poisoning have been reported in the tin-refining industry, seven of them fatal. The mortality rate of this small series is

therefore 28 per cent. It should be noted that this is one of the few industrial poisons which may kill outright.

In severe cases the first effects of haemolysis occur within six hours, when haemoglobinuria appears. Within 24 hours there is jaundice and by the third day anaemia in which the red-cell count may fall below 1,000,000 per c.mm. Death may occur from anuria in those cases in which the products of haemolysis lead to severe damage to the kidneys. Mild cases are often mistaken for food poisoning, and are accompanied by nausea, headache, shivering, exhaustion, giddiness, and vomiting. Reports of series of cases have often mentioned that a number of other men were affected, but not so severely as to require admission to hospital. It therefore seems possible that a number of cases too mild to present the classical picture of this form of poisoning may be occurring in industry and escaping detection.

The first essential in the prevention of this accident in industry is that all concerned, particularly works' managers and examining factory surgeons, should be fully alive to the danger of the processes involved and to the signs of early and slight poisoning. The workrooms should be ventilated and in confined spaces hazardous processes should be forbidden. Sometimes a breathing apparatus suitable for use in irrespirable atmospheres must be employed. Such an apparatus consists of an oro-nasal mask with tube connexion to the outer atmosphere. The wearer draws fresh air through the tube by his inspiratory efforts and expels the expired air through a valve in the mask. Further, as suggested by Koelsch (1920), a number of bird-cages containing small birds should be hung as near as possible to the work, since it is known from experience that the gas affects them before it affects man.

Dimethylarsine. The use of Scheele's green (cupric arsenite) in the preparation of artificial flowers and wall-papers has now only historical interest, because aniline colours have almost entirely taken the place of arsenic in these processes. When arsenical colours were used, as much as 60 gr. per square foot were found in samples of wall-papers examined; and such symptoms as coryza, conjunctivitis, gastro-enteritis, and tinglings in the extremities were found to be associated with residence in rooms papered with arsenical wall-papers. The mould *Penicillium brevicaulis* while growing in the paste split up the arsenic compounds, liberating from them a gas originally thought to be diethylarsine (Biginelli, 1901), but since identified as dimethylarsine (Challenger, 1935). In 1931 in the Forest of Dean a child died owing to inhalation of dimethylarsine from mouldy walls in a damp house. The source of the arsenic in this case was coke breeze, a constituent of the plaster of the walls. The use of concrete blocks containing this substance and the addition of arsenious oxide to cements to increase their rate of hardening are undesirable.

Mercury. Mercurial poisoning occurs in industry in three forms: (i) from exposure to the vapour and dust of metallic mercury, (ii) from contact, particularly of the skin, with mercury fulminate, and (iii) from exposure to

the vapour of organic mercury compounds and contact of these substances with the skin. The clinical picture is different in each of these three types.

Metallic mercury. Occupations giving rise to the risks of exposure to metallic mercury include mercury mining, recovery of the metal from the ore, separation of gold and silver from their ores by means of an amalgam with mercury, manufacture of barometers and thermometers and some types of electric meters and electric lamps, water gilding, in which an amalgam of gold or silver is applied to the object concerned and the mercury volatilized by heat, manufacture of surgical dressings containing mercury salts, bronzing of field glasses and photo-engraving, and the felting of fur and the manufacture of hard felt-hats (Legge, 1934).

Mercury vaporizes even at room temperature and, although there is no doubt that it can be absorbed through the unbroken skin, the use of the metal in industrial processes gives rise to poisoning mainly through the respiratory tract. In 1804 there was a fire in a quicksilver mine in Austria and mercury vapour escaped into the air and spread over the countryside; 900 persons in the neighbourhood had mercurial tremor and many cows suffered from salivation, cachexia, and abortion. But poisoning can occur from exposure to mercury at ordinary temperatures. In 1810 a British ship had some mercury containers broken in the hold. As a result all the birds and cattle on board died, 200 persons in the ship had symptoms of mercury poisoning, and three of them died.

The danger in the felt-hat industry arises from the presence in the air of workshops of fine fur which has been treated with nitrate of mercury in the process of felting. The fine hairs which form the fur of rabbits, hares, muskrats, and beavers are smooth, resilient, and straight. Treatment with some chemical substance which makes them limp, twisted, and rough greatly aids the felting process and many substances have been shown to produce such an effect. Among them is an acid solution of mercuric nitrate which is used in the preparation of hatters' fur in some countries.

The symptoms of mercurial poisoning arising in industry are as a rule slower in onset and more insidious in character than those which result from the continued internal administration of mercury. Further, two characteristic sets of symptoms which are never seen in medicinal cases occur in industrial cases, namely, tremor and erethism. Salivation and tenderness of the gums and mouth are usually early symptoms. The gums are swollen and bleed readily, but it is not easy to distinguish an early mercurial gingivitis from the pyorrhoea of a neglected mouth. Rarely a mercurial line is seen on the gums. It usually resembles the blue line due to absorption of lead but sometimes it is dark brown.

The most characteristic symptom, though it is seldom the first to appear, is mercurial tremor. It is neither so fine nor so regular as that of hyperthyroidism. It may be interrupted every few minutes by coarse jerky movements. It usually begins in the fingers, but the eyelids, lips, and tongue are affected early. As it progresses it passes to the arms and then to the

legs so that it becomes very difficult for a man to walk about the workshop and often he has to be guided to his bench. At this stage the condition is so obvious that it is known to the layman as the *hatters' shakes*. The tremor often passes away if the patient gives up his work before it has reached a serious stage. Alcoholism greatly favours its development and it is claimed that no total abstainer has ever suffered from tremor in severe form.

The symptoms known as *erethism* have been rare since silver took the place of mercury in mirror making. The man affected is easily upset and embarrassed, loses all joy of life, and lives in constant fear of being dismissed from his job. He has a sense of timidity and may lose self-control before strangers. Thus if a visitor stops to watch such a man in the factory, he will sometimes throw down his tools and turn in anger on the intruder, saying that he cannot work if watched. Occasionally a man is obliged to give up work because he can no longer take orders without losing his temper, or if he is a foreman because he has no patience with the men under him. Drowsiness by day, depression, loss of memory, and insomnia may occur, but under modern conditions hallucinations, delusions, and mania are rare (Hamilton, 1925).

In the manufacture of clinical thermometers and in laboratories where mercury is handled extensively, the benches should be covered with a smooth and impervious surface sloping in such a way as to drain the mercury into a suitable receptacle at the lowest point. The walls and floors should be of impervious material and the floor should be cleansed at the end of each day's work. Thermometers should not be filled without suitable exhaust-ventilation for the removal of mercury vapour. Overalls, mess-rooms, and washing facilities should be provided. The mouth and pharynx should be frequently rinsed with a mouth-wash and the teeth cleaned with a soft tooth-brush and a dentifrice. Periodical medical and dental examination can achieve a great deal, especially by emphasis on the proper hygiene of the mouth. Cavities in carious teeth should be filled, sharp angles smoothed, and useless teeth extracted (Legge, 1934).

In the furriers' workshops of the hat trade the technical processes of carrotting, drying, brushing, sorting, and packing are carried out; if the fur cutting shops are small, cheaply built, and badly managed, poisoning will readily arise. Exhaust ventilation and spotless cleanliness must be introduced in such shops. These measures may not eliminate all risks, for after the carrotted fur has left the furriers' workshops it goes through further processes known as blowing, forming, hardening, sizing, blocking, shaping, crown and brim ironing, planking, proofing, stoving, and pressing. In Great Britain preventive measures have reduced the number of cases of poisoning to negligible proportions, but there are still many in Italy. Russia has abolished the use of mercury and substituted a potash method for the felting of fur, but this produces felt of inferior quality. A harmless substitute for nitrate of mercury was recently introduced into the industry in the United States of America (Beal, McGregor, and Harvey, 1941).

Mercury fulminate. Mercury fulminate is handled in explosives factories where detonators and percussion caps are made. It is obtained by reaction on alcohol of a solution of mercuric nitrate in excess of nitric acid. The following workers are exposed to risk—fillers, packers, cleaners, cap loaders, pressers, dryers, sievers, mixers, decanters, and inspectors. In one process wet fulminate of mercury is spread out by hand on cloths placed on a hot table. One end of the cloth is then raised, and the powder tilted to the other end. In a later process the fulminate is passed through sieves of horsehair to obtain the fine powder necessary for the caps. The fine dust falls upon the skin and dermatitis follows. In one department operatives moisten the material with methylated spirit, work it with the fingers, and then press it into moulds.

The skin of most of those employed in mixing, drying, filling, and preparing the composition shows characteristic lesions. The susceptibility of some individuals is such that they cannot stand it for a day, whereas others suffer only in warm weather. As a rule the cases of *fulminate itch*, as they are called in the trade, are slight. Generally the uncovered parts of the body are attacked by an erythema accompanied by intense itching, swelling, and oedema, particularly on the face, eyelids, neck, behind the ears, and on the forearms. Erythematous papules break out on the inflamed areas and may become vesicles, bullae, and pustules. A pustular folliculitis often develops on the hairy parts of the skin (Koelsch, 1930). The fulminate may lodge in a crack or abrasion of the skin and act as a corrosive, causing small painful necrotic lesions on the hands, especially the tips of the fingers, which last about a fortnight (MacLeod, 1916). The operatives call them *powder holes*. If the fulminate attacks the knuckles or the roots of the nails ulceration may penetrate to the joint and bone. Exceptionally the whole body is affected. Recovery takes place in from one to two weeks and is accompanied by desquamation.

The superficial mucous membranes also are irritated in persons carrying out sieving operations. After staying a short time in the rooms where this work is done slight pricking of the eyes and nose is felt with an inclination to sneeze, and irritation of the throat. The conjunctivae, nose, and larynx may become inflamed. The majority of workers are careless of their dental toilet and their teeth become blackened owing to the formation of mercury sulphide.

In the manufacture of mercury fulminate meticulous attention should be paid to detail in all matters of cleanliness in the plant. The gases formed in the preliminary processes should be either condensed or removed to the outer air well above the heads of the workers. Substitution of machinery for hand labour is impossible on technical grounds. In the rooms where the detonators are filled with the composition, the fume resulting from the numerous small explosions should be removed by means of mechanical ventilation. All persons employed should be provided with well-fitting overalls, caps, and rubber gloves, and if necessary respirators. The face and

other parts of the body should not be rubbed with soiled hands. Washing accommodation should be provided close to the work-room, and a separate towel provided for each worker. The hands and arms should be washed in a 10 per cent. aqueous solution of sodium thiosulphate before meals and before leaving work.

In some factories work-people coming into contact with mercury fulminate are given ointment wherewith to restore softness to the skin after washing. Such ointments contain lanolin, and either sodium carbonate, balsam of Peru, or phenol (White, 1934). Periodical medical examination is important, and in the first instance persons with delicate skins and those who have suffered from skin diseases must be rejected. Regular dental examination can achieve much, especially by emphasis on the hygiene of the mouth. Whenever powder penetrates the skin through an abrasion or cut, it must be washed in a 10 per cent. aqueous solution of sodium thiosulphate. For the conjunctivitis a 2 per cent. solution of this substance as an eyewash has been beneficial (Legge, 1934).

Organic mercury compounds. Organic compounds of mercury were first used in chemical research in 1863, in therapeutics in 1887, and in the manufacture of seed dressings and other fungicides in 1914. Those with hydrocarbon groups of low molecular weight have been found the most toxic, and the only cases of systemic poisoning recorded in man have been due to methyl and ethyl derivatives.

Frankland and Duppa (1863) used di-methyl mercury in the course of some research work undertaken at St. Bartholomew's Hospital to determine the valency of metals and metallic compounds, and two laboratory technicians engaged in this work developed symptoms of poisoning and died (Edwards, 1865, 1866). One of them was a German aged 30 years who had been exposed to di-methyl mercury for three months. He complained of numbness of the hands, deafness, poor vision, and sore gums. He was found to be slow and dull in manner, unsteady in gait, and unable to stand without support. There was no motor palsy, and the fundi were normal. Within a week he became rapidly worse, restless, unable to answer questions, incontinent of urine, and comatose. He died two weeks after the onset of symptoms.

A second technician, aged 23 years, had worked in the laboratory for 12 months and had handled di-methyl mercury for a period of two weeks only. Four months after this exposure began he complained of sore gums, salivation, numbness of the feet, hands, and tongue, deafness, and dimness of vision. He answered questions only very slowly and with indistinct speech. There was ataxia, but no weakness of the upper limbs. Three weeks later he had difficulty in swallowing, was unable to speak, had incontinence of urine and faeces, and was often restless and violent. He remained in a confused state and died of pneumonia 12 months after the onset of symptoms. A third technician was affected with symptoms similar in character but less severe. He eventually recovered. The story of these deaths has been handed down verbally from one generation of chemists to another.

In 1887 Hepp used hypodermic injections of di-ethyl mercury in the treatment of syphilis. He gave doses ranging from 0.1 to 1.0 c.c. of a one per cent. solution of this substance. No patient received more than two injections, for in the meantime animal experiments had been carried out which suggested that the substance was highly toxic. The picture of di-ethyl mercury poisoning in animals was found to differ from that of poisoning by inorganic mercury compounds. There was only moderate inflammation of the intestinal tract, but the nervous system was constantly involved. An ascending paralysis was combined in some animals with ataxia. Inco-ordination of movement was noticed especially in rabbits, and motor paralysis in dogs and cats. Tremor, blindness, loss of sense of smell, transient deafness, and attacks of wrath on the slightest provocation were also noticed in many of the dogs.

Seed-borne diseases of cereals were first treated by organic compounds of mercury in 1914. To-day their use in the prevention of such diseases as bunt of wheat (*Tilletia tritici*), covered smut of barley (*Ustilago hordei*), leaf stripe of oats (*Helminthosporium avenae*), and leaf stripe of barley (*Helminthosporium gramineum*), is a well-established principle of plant hygiene (Martin 1936).

The relationship between the molecular structure and the fungicidal activity of organic compounds of mercury has been investigated. Richm (1923) determined the minimum concentration of different compounds necessary to inhibit germination of bunt spores under standard conditions. Gassner and Esdorn (1923) used a similar method and were able to demonstrate the importance of molecular structure in determining the fungicidal properties of these compounds. Thus, inhibition of germination under standard conditions was produced by different compounds in the following proportion—mercuric chloride 0.025, chlor-phenol mercury 0.07, and methyl mercury iodide 0.001.

Methyl mercury iodide was thus the most active of the compounds tested, but was discarded by these authors on the score of its highly poisonous character. Weston and Boer (1935), employing tolyl, ethyl, phenyl, and methyl mercury compounds against a large number of seed-borne diseases of cereals, confirmed the view that the fungicidal properties decrease with increase of the molecular weight of the hydrocarbon group.

The manufacture of phenyl and tolyl mercury compounds in large quantities by the chemical industry in this country and in Germany has been carried on by automatic methods in enclosed apparatus. The products are used mainly in the form of dusts, though sometimes they are employed in solution. So far as is known, no mishap worse than an occasional burn on the skin has occurred in handling them. If an organic mercury compound comes in contact with the skin, warmth and redness occur after six hours, and blistering after 18 to 24 hours. The blister contains serous fluid, and the lesion remaining after it bursts may take three weeks to heal.

In 1940 Vintinner described 42 cases of dermatitis among lumbermen

who were applying a fungicide to newly cut timber in order to combat stain-producing fungi. The substance used was an aqueous spray containing one part in 6,600 of ethyl mercury phosphate. The hands and forearms of all but a small percentage of the men exposed became red and swollen, and then covered with blebs more than an inch across, simulating burns. The disability lasted from five to 30 days.

In 1940 Hunter, Bomford, and Russell recorded four cases of poisoning by inhalation of methyl mercury compounds in a factory where fungicidal dusts were manufactured without the use of enclosed apparatus. The cases were unique because they occurred in the only factory where these substances have ever been made, and they are unlikely ever to be made again. With the exception of tremor, the symptoms of poisoning by metallic mercury, namely, salivation, stomatitis, and erethism, were absent, and the nervous system alone was involved. There was severe generalized ataxia, dysarthria, and gross constriction of the visual fields, while memory and intelligence were unaffected. The illness of these men was comparable to that of the two technicians who died at St. Bartholomew's Hospital. Experiments on rats and a monkey confirmed the selective effect of methyl mercury iodide and nitrate on the nervous system. There was an intense and widespread degeneration of certain sensory paths of the nervous system, the peripheral nerves and posterior spinal roots being affected first, the posterior columns and the granular layer of the middle lobe of the cerebellum later.

In 1943 Hill reported the death, in Canada, of two girls who were stenographers in a warehouse which stored di-ethyl mercury for use as a fungicide. Their desks were about 15 feet from a stock pile of 20,000 pounds of the fungicide, and at a point 3 feet from the di-ethyl mercury and $3\frac{1}{2}$ feet from the floor the atmosphere contained 2.7 mg. of mercury per cubic foot of air. Exposure had occurred for six months, but no clinical details were given.

In the manufacture of organic mercury compounds adequate precautions must be taken to ensure that dusts and vapours do not come in contact with the skin and are not inhaled. The use of gloves and respirators is inadequate as a means of protection; the whole process of manufacture, including the final packing of the dust, should be carried out mechanically. Compared to the factory worker the farmer runs little risk. He should be warned that mercurial dressings are poisonous, and should obtain seed which has already been dressed in an enclosed apparatus.

The ataxia and dysarthria of methyl mercury poisoning must be treated by re-educative movements such as teaching the patient to walk on chalked lines. An expert in charge of a speech clinic with patience and the use of a mirror may teach him to speak; and with perseverance in some cases the patient may be taught to use knife, fork, pencil, and even a typewriter.

THE AROMATIC COMPOUNDS

The coal-tar derivatives are so numerous and complex that it is difficult for the toxicologist to keep pace with the chemists who produce them. The following compounds will be discussed—benzene, nitrobenzene, dinitrobenzene, trinitrotoluene, dinitrophenol, aniline, tetranitromethylaniline, phenylenediamine, and tri-*ortho*-cresyl phosphate.

It is sometimes possible to predict from the chemical composition of the simpler members of this group what their physiological action is likely to be. Addition of a *nitro*- or *nitroso*-group usually produces a more toxic compound, but it does not follow that toxicity will continue to increase as more *nitro*-groups are added. Thus 2-4 dinitrophenol is toxic, whereas trinitrophenol is practically harmless. The position of the substituent groups in the benzene ring may have an effect on the toxic action. Thus the toxic properties of 2-4 dinitrophenol are not shared by any of the other isomers. When a *nitro*-compound is reduced to an amine, as when nitrobenzene is reduced to aniline or nitrotoluene to a toluidine, the toxic character remains much the same, but the intensity of the action is lessened. Sulphonation renders a compound non-toxic; as soon as aniline is sulphonated it ceases to give trouble (Hamilton, 1925). But there is no inflexible rule for judging the toxicity of isomers. Where the substituent group is in the *para*-position the compound is likely to be more toxic than the corresponding *ortho*- or *meta*-isomer (Fraenkel, 1912). This is true of *para*-phenylenediamine, but in the case of tri-cresyl phosphate the *ortho*-isomer is the toxic one, and *meta*-nitraniline is more poisonous than *para*-nitraniline. Toxic activity depends not only on chemical constitution, but also on physical properties. It may be that toluene is harmless compared to benzene merely because of its higher boiling point and lower vapour pressure.

Benzene. Benzene, a hydrocarbon of the aromatic series and a coal-tar product, is a colourless liquid with a distinctive odour. It must be carefully distinguished from benzine, a mixture of varying proportions of aliphatic hydrocarbons, chiefly hexane and heptane, which is a distillate of petroleum.

Commercial benzoles contain toluene and xylene, and traces of phenol, carbon disulphide, and other substances. Benzene is handled in industry in two distinctly different ways. In the first, it is used in large quantities in closed mechanical systems, and the industries involved include the distillation of coal and coal tar, the blending of motor fuels, and the chemical industries. In the second, it is used as a solvent or diluent, and the industries involved include the rubber industry, the manufacture of paints and varnishes, the aeroplane, linoleum, and celluloid industries, the manufacture of artificial manure and glue, and the extraction of certain alkaloids.

Of all the hydrocarbons benzene is outstanding because of its serious toxic effect on the bone-marrow. Any doubt that this effect is due to impurities in crude benzoles has now been settled. The response of dogs and guinea-

pigs exposed to crude and commercial benzoles is characteristic of benzene poisoning and the physiological effect is due primarily to the benzene content of the solvent used and not to impurities (Schrenk, Yant, Pearce, and Sayers, 1940). Toluene, the higher homologues of benzene, and petroleum distillates containing no benzene have no such action. Commercial toluol may contain up to about 15 per cent. of benzene, and this may explain serious toxic effects in industrial workers which have been attributed to the inhalation of toluene. Many of the distillates both of coal tar and petroleum exert dangerous acute narcotic effects, and the outcome may be fatal if they are inhaled in sufficient concentration; under industrial conditions, however, only benzene and mixtures containing benzene produce aplastic anaemia. The risk of poisoning from this group of industrial solvents depends, therefore, on their benzene content.

The greater volatility of benzene as compared with its higher homologues has obvious commercial advantages in aiding quick drying of paints, lacquers, and rubber cements. This is an obstacle to the substitution of the higher homologues for benzene. Much, however, has been achieved in this direction in Great Britain, particularly in the rubber industry and in the manufacture of cellulose lacquers. Up to 1939 it was rare for more than one or two cases to be notified annually. At the present time, pressing need for aircraft has increased the risk of benzene poisoning since workers in aircraft doping are exposed to sprays containing 10 to 15 per cent. of benzene.

Except for a few cases of accidental or suicidal ingestion, poisoning in industry is due to inhalation of the vapour of benzene. Acute poisoning results from cleaning vats, painting tanks, or the breakage of distilling apparatus. The symptoms are excitement, incoherent speech, flushed face, headache, giddiness, nervousness, insomnia, nausea, paraesthesiae in the hands and feet, and fatigue which may persist for more than two weeks. If the exposure is continued narcosis and ultimately death will follow. Muscular exertion, emotion, and fear are believed to increase the severity of the intoxication.

Treatment consists of rest, warmth, artificial respiration, administration of oxygen and carbon dioxide mixture through a B.L.B. mask, and injection of nikethamide as a respiratory stimulant. After recovery the patient should not return to work for some days for fear of relapse.

The early work on chronic benzene poisoning (Santesson, 1897; Selling, 1910, 1916) established the conception of a simple, constant clinical picture. This was an over-simplification based on insufficient human material. The attack on the bone-marrow was destructive, affecting first the platelets, then the granular leucocytes, and finally the red cells. The settled belief grew up that a diagnosis of benzene poisoning is not justified unless the blood picture shows an aplastic anaemia associated with a granulocytopenia; that a leucopenia is more important in diagnosis than a low red-cell count; that cases of benzene poisoning invariably show purpuric manifestations

associated with bleeding gums, epistaxis, or menorrhagia; that the spleen is never enlarged in these cases; that at autopsy the bone-marrow is always in a state of aplasia; that young women are more susceptible than men to the vapour of benzene; and that a concentration of 100 parts per 1,000,000 or less in the air may be considered safe.

It is true that some advanced cases do show many of these features. However, in 1934, when only 30 cases of industrial benzene poisoning had come to necropsy, Hamilton prophesied that when the blood pictures in this disease had been studied as intensively as those produced by radium or X-rays they would show the same infinite variety. In 1939 a series of detailed studies appeared which not only fulfilled her prophecy, but swept away many long-cherished beliefs about benzene poisoning.

These studies were all undertaken upon workmen exposed to benzene and were published by Hunter, who investigated 89 cases, by Erf and Rhoads, who investigated nine cases, and by Mallory, Gall, and Brickley, who examined histological sections from 19 cases, 14 of these being necropsies and five biopsies. The authors last mentioned found the picture in the bone-marrow to vary from severe hypoplasia to the most extreme hyperplasia, and they even recorded extramedullary haemopoiesis. In spite of the old view hyperplasia proved the more common of the two reactions. It was found only in patients with prolonged exposure, whereas hypoplasia followed either short or long contact. Sex appeared to play a part, for hyperplastic reactions were distinctly more common in the male, and hypoplastic ones in the female subject. Although splenomegaly was rarely apparent clinically, the spleen was often enlarged at autopsy. Lymph nodes were frequently prominent and dusky-pink on cut section, but occasionally they were grossly enlarged. Purpura of the skin, mucous membranes, and serous surfaces was often noticed. Gangrenous stomatitis was present in some of the worst cases.

There are many indications that circulating red cells may be destroyed at an abnormally rapid rate in patients poisoned with benzene. Many authors have recorded increased numbers of circulating reticulocytes, a finding which was assumed to indicate abnormally active haemopoiesis. The plasma-bilirubin is raised and an increased excretion of urobilinogen in the urine has been reported. Haemosiderosis of the liver, spleen, kidneys, and bone-marrow is a frequent pathological alteration, both in human beings and in experimental animals dead of benzene poisoning.

In the cases reported by Erf and Rhoads the haematological findings were very variable. Thus, in nine patients the haemoglobin values ranged between 47 per cent. and 81 per cent., the red-cell count from 1,850,000 to 4,130,000 per c.mm., the white-cell count between 1,750 and 6,500 per c.mm., the platelet count from 18,000 to 150,000 per c.mm., and the reticulocytes from 3.8 to 14 per cent. Free hydrochloric acid was found in the gastric juice of all the patients, though two were achlorhydric until histamine was injected.

From experience of the colour-printing industry in which benzene is used as an ink solvent, Greenburg, Mayers, Goldwater, and Smith (1939) deprecated reliance on the leucocyte count as a rapid means of detecting cases of poisoning; leucopenia, they said, is more often found in severe than in early cases. They regarded a reduction in the number and an increase in the size of the red cells as earlier and more sensitive signs of poisoning, and they looked with suspicion on a macrocytosis in a benzene worker even in the absence of other abnormalities.

Eosinophilia, erythrocytosis, and leucocytosis occasionally accompany the condition, but rarely stand as isolated phenomena. Of the 98 cases quoted above, 24 had an eosinophil count over 3 per cent., seven had a red-cell count over 5,200,000 per c.mm., and 28 had a white-cell count over 9,900 per c.mm.

The evidence that chronic exposure to benzene produces leukaemia in human beings is still incomplete, but it is accumulating rapidly and to a volume which commands serious consideration. Penati and Vigliani (1938) were able to collect 10 cases of leukaemia in patients exposed to benzene. All varieties of the leukaemic state have been recorded—chronic myeloid, chronic lymphatic, and acute myeloblastic. Four more cases may now be added to this list, namely two published by Hunter, one by Mallory, Gall, and Brickley, and one by Erf and Rhoads, all in 1939. One of Hunter's patients showed a typical acute leukaemia; he had been heavily exposed to benzene for four years, lightly for a further six years, and not at all for the 20 months before his illness. Mallory tells of leukaemia in a boy of 12 years who repainted his toys after taking off the old paint with a solvent found to contain benzene. Fourteen cases of leukaemia developing among the many thousands of people exposed to this solvent do not seem impressive, but they gain in significance when we bear in mind that Lignac (1932) produced leukaemia in mice poisoned with benzene. Salter (1940) suggested that the leukaemia may be due to a tumour of the bone-marrow in which benzene plays the role of a carcinogen.

Victims of benzene poisoning often constitute a small minority of the workers. A single susceptible individual may develop fatal poisoning in an environment which does not give rise even to mild poisoning in others (Ronchetti, 1922). The factors responsible for the great variations in susceptibility are unknown, but the original idea that women are more susceptible than men has been disproved (Hunter, 1939). Changes in the blood may begin from two days to one month after the first exposure and may progress or develop after exposure has ceased.

Death may occur within three weeks of the onset of symptoms. The death rate is as high as 10 per cent. Occasionally a severe case ends in recovery. Hayhurst and Neiswander (1931) recorded a case in a rubber worker in whom the red cells were 900,000 per c.mm., haemoglobin 10 per cent., white cells 850 per c.mm., bleeding time more than 25 minutes, and platelets 100,000 per c.mm. Treatment by blood transfusion and iron was followed

by recovery, and three and a half years later the blood count was normal except for slight granulocytopenia.

The prolonged inhalation of any concentration of benzene is dangerous, but poisoning could be prevented by abandoning its use as a solvent, and from medical investigators all over the world comes the plea to use one of the many harmless substitutes. Certainly benzene should be used only under the best conditions of ventilation, and its characteristic odour in a workshop should be regarded as a danger signal. No patient who has suffered from poisoning should return to work involving exposure to benzene. Patients with chronic poisoning should be treated by repeated blood transfusions since the toxic influence may persist even after removal from exposure. The response to treatment is poor.

Aromatic nitro- and amino-derivatives. Most of the aromatic *nitro-* and *amino-*derivatives, and especially nitrobenzene, dinitrobenzene, and aniline act on the blood converting haemoglobin into methaemoglobin. For record purposes the convenient terms *anilism* or *anilinism* are sometimes used to cover all cases in which methaemoglobinaemia has occurred from exposure to any one of this group of substances.

Methaemoglobinaemia leads to cyanosis of a distinctive tint, most noticeable on the cheeks, ears, tip of the nose, and finger-nails. It is a bluish-grey colour varying in intensity from lilac to a deep leaden hue, and quite different from the blue colour of cyanosis due to lack of oxygen. Since methaemoglobin cannot transport oxygen, tissue anoxia results. On the other hand, the normal haemoglobin is fully saturated with oxygen, and, therefore, the arterial oxygen tension is not significantly reduced. However, the consumption of oxygen by the tissues causes a marked diminution in the venous oxygen tension.

Much of the work done on methaemoglobinaemia has produced contradictory results. This arose through difficulties in the accurate identification and quantitative determination of methaemoglobin in the blood. Price-Jones and Boycott (1909) thought that methaemoglobin disappeared by the time cyanosis was fully developed, but Schmidt (1930) stated that the bands of methaemoglobin appear only when 40 per cent. of the oxyhaemoglobin is transformed into methaemoglobin, and that death occurs when 75 per cent. of the oxyhaemoglobin is transformed. Then, in 1932, Peters and Van Slyke in work upon acute nitrobenzene poisoning suggested that the pigment formed is some other haemoglobin derivative, possibly a direct combination with nitrobenzene.

In 1938 Hamblin and Mangelsdorff published an accurate method for measuring the percentage of methaemoglobin in venous blood. Using a recording spectrophotometer, they demonstrated methaemoglobinaemia in concentrations varying from 1 to 100 per cent. These authors made a large number of methaemoglobin measurements on the blood of patients who had been exposed to nitrobenzene, dinitrobenzene, aniline, dimethylaniline,

paranitraniline, and mixed toluidines. In every case the severity of the clinical picture increased in direct proportion to a rising concentration of methaemoglobin and decreased with a falling concentration.

It was shown by Malden as early as 1907 that punctate basophilia of the red cells is as valuable an early sign of poisoning by dinitrobenzene and aniline as it is of lead poisoning.

Unlike most other industrial poisons, the aromatic *nitro-* and *amino-*derivatives are absorbed not only through the respiratory tract, but also through the skin. The importance of the skin as a channel of absorption was shown for dinitrobenzene in 1901 by White and Hay, and for trinitro-toluene in 1918 by Moore. These investigators rubbed their own skin with the substance to be tested.

It has often been observed clinically that the poisonous effect of the aromatic *nitro-* and *amino-*derivatives is increased by the simultaneous intake of alcohol even in relatively small amounts.

Nitrobenzene. Nitrobenzene or mononitrobenzene is referred to in commerce as oil of mirbane, or artificial oil of bitter almonds. It is an oily liquid almost colourless or faintly yellow, with an odour of bitter almonds which is still present in great dilution. It is used in the manufacture of aniline dyes and explosives, as a constituent of shoe polish, floor polish, and on account of its odour as a perfume in cheap soaps and other toilet articles. It is even used as a substitute for the natural essence of bitter almonds in confectionery and liqueurs.

Nitrobenzene is regarded by experienced men as more dangerous than aniline. The most important portal of entry is through the skin, but the respiratory and digestive tracts may be responsible. In acute occupational poisoning skin absorption occurs from the wearing of clothes badly soiled by splashing, or from lack of cleanliness on the part of the workman who does not change his working clothes sufficiently often.

Hamilton (1919) recorded the case of an elderly man who was at work in a soap factory in Boston, carrying a five-gallon can of oil of mirbane. He spilt some of the fluid on his trousers, became shaky, and suddenly collapsed, spilling more of the fluid on himself. His mirbane-soaked clothing was not removed before he was sent to hospital, and it is not surprising that his condition was serious when he arrived there. He was unconscious, with slow irregular breathing but a good pulse. The pupils were small, irregular, and fixed. The skin was a pale, grey-blue colour. Some blood withdrawn from a vein was as brown as chocolate. Respiration failed but the pulse was good until just before death, which occurred one hour after admission.

Nitrobenzene is more poisonous to the nervous system than is dinitrobenzene. The symptoms include fatigue, vertigo, headache, vomiting, general weakness, buzzing in the ears, and numbness in the limbs. In serious cases there is loss of consciousness followed by deep coma in which the pupils are contracted at first and react sluggishly to light, but later dilate and react no more. The pulse is rapid and weak, and the skin damp and cold.

Respiration is quickened at first, but it slows as the patient becomes unconscious. Death may supervene during profound coma. In patients who recover, consciousness returns generally in the first 24 hours. The pulse and respiration improve, but the nervous symptoms may persist for a week or more.

The blood changes include conversion of haemoglobin into methaemoglobin, and this gives rise to the characteristic lilac cyanosis. In grave poisoning the number of red cells may drop in six days to 2,000,000 per c.mm., with a diminution in the content of haemoglobin to as little as 30 per cent. Polychromatophilia, punctate basophilia, anisocytosis, and poikilocytosis are found, and where the anaemia is severe normoblasts may appear. The colour index may be high for a time. The worst stage of the anaemia is usually passed by the end of the first or second week, and thereafter the blood count returns rapidly to normal.

About the third day there may be jaundice and the spleen may be slightly enlarged. At the end of the second week the jaundice persists only in the conjunctivae and gives place to the pallor of anaemia. The enlargement of the spleen disappears after several weeks as the blood count returns to normal. Sometimes, after the poisoning has been overcome, there is a reactive erythrocytosis with a red-cell count as high as 7,000,000 per c.mm.

In serious cases the urine may have a pronounced odour of nitrobenzene. It may show a dark brown tint from the presence of methaemoglobin, and this colour may deepen still more on the surface on exposure to air. Albumin and casts may be found, and in the jaundiced cases bilirubin is present.

Subacute and chronic forms of poisoning may follow upon repeated absorption of small doses of nitrobenzene. Anaemia is the leading feature of the clinical picture and pallor is a more prominent sign than in aniline workers. If cyanosis is present it disappears rapidly after cessation of work. Fatigue, headache, and loss of appetite are commonly seen. Redness and swelling of the exposed skin and even a pustular eruption have been recorded. Complete recovery from the anaemia and the nervous symptoms may require several weeks (Engel, 1934).

For reasons of health it is necessary in the manufacture of nitrobenzene to use closed apparatus. Transport, as well as the emptying of receptacles, should be effected either by the use of compressed air or by aspiration. Good natural ventilation should be provided and, in hot weather, this must be artificially reinforced. Floors should be impermeable and not made of asphalt or tar, because these materials absorb the toxic substance. The workman should be provided with suitable clothing, and this should be changed so often that it does not become unduly impregnated with nitrobenzene. Gloves are necessary and should be frequently changed and cleaned. Cloak-rooms, washing-rooms, and baths are essential. Workmen should be instructed as to the care of any victim of an accident in which the clothing becomes suddenly soaked with the liquid. It is imperative that such a workman should have his clothes removed and be given a bath at once.

All workers should be informed of the danger which may follow indulgence in alcohol. Regular medical inspection of workmen is desirable and medical assistance should at all times be within easy reach.

Dinitrobenzene. Of the three isomers of dinitrobenzene, it is only *meta*-dinitrobenzene which is used commercially. It is a solid at ordinary temperatures and, in the pure state, it forms inodorous, colourless flakes. The commercial product is slightly yellow. It is used extensively in the manufacture of dyes and explosives. Owing to its deficiency in oxygen its explosive properties are not marked and detonation is difficult to bring about. Mixed with potassium chlorate, dinitrobenzene forms *cheddite*, with ammonium nitrate, *roburite*, and with guncotton, a smokeless powder called *indurite*. A mixture of potassium chlorate and dinitrobenzene is known in the United States of America by the expressive name of *rack-a-rock*.

Since dinitrobenzene is a solid, cases of poisoning develop less rapidly and are less severe than in the case of mononitrobenzene. Poisoning occurs among men who either shovel or melt dinitrobenzene. An attack usually develops some hours after a man has left the plant and rarely during work. Skin absorption was proved by White and Hay as early as 1901. Hay gives the following account of the experiment performed upon himself: 'On Oct. 8th, before dressing, I anointed my groins with a small portion of the 25 per cent. dinitro-benzene ointment, weight 400 milligrammes, containing 0.1 gramme of dinitro-benzene. I repeated this in the evening before going to bed. On the 9th I noticed very marked blueness about the lips and the finger nails; the tongue was also markedly blue. There were no subjective sensations. Before dressing I anointed my groins again with a similar quantity, but at 12 noon, owing to the cyanosis increasing in intensity, I carefully washed off all the ointment. At 1 p.m. the lips were a livid blue and the nails and skin generally of a deadly hue. The pulse was 100 to 120; it was regular in time and force and with its tension apparently raised and fuller. There was a feeling of fulness in the head and some throbbing headache, increased by movement. There was no obvious alteration in the urine. On cutting the thumb the blood appeared of a distinctly brown and darker colour than is normal. . . . At 6 p.m. the pulse was still full and bounding, from 96 to 98, regular in time and force. There were a rather metallic taste in the mouth and frontal and orbital headache, accompanied by a feeling of fulness, increased by movement, especially when running up and down stairs. Oxygen was inhaled for five minutes without any relief or alteration in the appearance of the lips and skin. The veins of the hands and the ears were full and engorged. A distinct tremor of the hands was present. On the 10th there was still some cyanosis of the lips, but not so marked as on the 9th. The headache had almost disappeared and there was no tremor. The pulse was still somewhat frequent. On the 11th my health was practically normal with the exception of a slight tendency to headache.'

The main effect of dinitrobenzene is the conversion of oxyhaemoglobin into methaemoglobin. This may progress to the extent of making the blood

a chocolate colour. Spectrophotometric measurements show that the severity of the clinical picture increases in direct proportion to the rising concentration of methaemoglobin in the blood. Malden (1907) described the blood counts in 21 men engaged in the manufacture of dinitrobenzene. The red cells were reduced in numbers and showed marked punctate basophilia. The haemoglobin was proportionately decreased, the colour index being normal. The total white cells were increased, but with a relative decrease in the polymorphonuclear cells. Dinitrobenzene undergoes in the body a change into *meta*-nitraniline, and is eliminated in this form by the urine (Lipschitz, 1920). In addition, methaemoglobin, haematoporphyrin, haemoglobin, and sometimes albumin, have been found in the urine. A workman may notice that he passes smoky urine soon after his first contact with dinitrobenzene.

In acute poisoning there is rapid onset of headache, vertigo, and vomiting. Depression is followed by exhaustion, numbness of the legs, a staggering gait, somnolence, and then loss of consciousness. Profound bluish-grey cyanosis develops and the skin is moist and cold. Respiration becomes fast and deep, the pulse is weak and rapid, and the blood-pressure drops. If consciousness is lost the pupils become dilated, the temperature falls, and death may occur within 24 hours from central respiratory paralysis. If acute poisoning terminates in recovery the symptoms remain much longer than in poisoning by aniline. There is more exhaustion, and cyanosis and vertigo may persist for days or weeks, whereas in aniline poisoning a man recovers in 48 hours.

In subacute and chronic poisoning secondary anaemia is a prominent feature. Jaundice is unusual. When it appears it produces a peculiar appearance owing to the co-existence of pronounced cyanosis. In cases where jaundice is very deep, enlargement of the liver has been detected. Rarely death has occurred from acute necrosis of the liver (Engel, 1930).

In Bavaria from 1915 to 1918 there were fully 1,000 cases of dinitrobenzene poisoning. Many of the victims had from two to five attacks and there were 113 deaths. In Great Britain before 1914 there were only two or three factories making *nitro*-derivatives of benzene. The factory where the manufacture was on the largest scale gave rise to more anxiety than any other, since there was not sufficient other employment to allow alternation of work. One factory had to close during a hot summer because there were not enough healthy men left to carry on the work. In another factory hot weather, inadequate ventilation, and overtime led to 28 cases of illness with two deaths in the course of a few weeks. With reduction of contact to four hours a day no further cases occurred (Legge, 1917).

In building a factory which is to be perfect from both technical and hygienic points of view it is important that doors, windows, walls, partitions, and platforms should be so arranged as to allow of free natural ventilation. Nitration tanks should be provided with air-tight lids for charging and with adequate exhaust ventilation. Special attention must be paid to the removal

of steam containing the toxic substance. All flooring should be even and made of an impermeable material. These arrangements may fail in summer and on windless days, when the heat is oppressive. On such days it is not uncommon to see the whole personnel of a dinitrobenzene factory affected with slight cyanosis.

There must be a constant campaign against careless and dirty habits. Working garments, gloves, and boots must be changed and cleaned regularly as soon as soiled by the poisonous product. Cloak-rooms and baths must be provided and stress laid upon the urgent necessity for changing at once and taking a bath whenever the garments have been soiled more than usual. Workmen who do not change their working clothes on returning home may sit before the fire and absorb dinitrobenzene from the evaporation of crystals or from the material in solution on their clothing. Absorption from the alimentary canal is more rapid if the stomach is empty, and it is therefore desirable that men should have a meal before they begin work. Clear warning should be given as to the danger of taking alcohol even in ordinary amounts. On account of the frequency of subacute and chronic poisoning strict medical supervision is of great importance.

Trinitrotoluene. 2-4-6 trinitrotoluene or α -TNT is a pale yellow crystalline solid. Commercial TNT is handled in blocks from which an objectionable oily exudation arises as a result of impurities, including small amounts of other trinitrotoluenes and traces of dinitrotoluene. The wide adoption of TNT as an explosive is indicated by its many synonyms which include such names as *trilit*, *trinol*, *tritolo*, *triton*, *trolite*, *trotyl*, and *Füllpulver-02*. Its main use is as a bursting charge in shells, bombs, and mines. Owing to its very marked deficiency in oxygen it is more often used mixed with substances rich in oxygen; *amatol* and *ammonal* contain ammonium nitrate and *baratol* contains barium nitrate.

The main route of absorption of TNT is through the skin, but, of course, ingestion of the substance and absorption through the respiratory tract of dust and fume cannot be ignored. The fate of TNT in the body has been studied, but with little result. In 1916 Webster devised a test for a derivative of TNT, namely 2-6 dinitro, 4 hydroxylamino-toluene, which is excreted in the urine. Webster and others have since improved the test, making it sensitive to 1 part in 10,000 (Ingham, 1941). The urine of practically all workers in TNT contains the substance identified by Webster, but in some there is only a minute trace, in others an intense reaction, and there may be a considerable reaction where there is no sign of TNT illness, or illness with only a moderate degree of reaction.

In 1917 Legge satisfied himself by studies of the precise occupation of workers with toxic jaundice that the skin had been the route of absorption. Moore (1918) investigated the problem of skin absorption of TNT by experiments upon himself. After showing that the Webster test of his urine was negative he went into an orchard attached to a factory and rubbed into the palms of his hands intermittently for about six hours an *amatol* pellet

containing 20 per cent. TNT. He was careful to refrain from going near any part of the factory where there was TNT dust or fume. After two hours a specimen of urine was passed and this showed a positive Webster test. This reaction went on increasing until next day when there was quite a strong reaction lying in intensity about at the average given by the urine of the shop worker. The TNT reaction remained and gradually increased in intensity for a period of 10 days, although he neither rubbed TNT in again nor went near any source of dust or fume. The first morning after rubbing in the *amatol* he woke with all the symptoms of a minor attack of TNT illness. He had marked frontal headache with a feeling of nausea and intermittent abdominal pain. This abated shortly, but a feeling of malaise and drowsiness persisted for about two days. After a fortnight, and when his urine had become free from TNT reaction, he repeated the experiment with the same result as before.

The clinical manifestations of TNT poisoning include dermatitis, cyanosis, gastritis, toxic jaundice, and anaemia. The hands and sometimes the face and hair are stained orange with TNT, causing an appearance easily distinguishable from jaundice. Dermatitis arises on the parts exposed, namely the hands, forearms, legs, wrists, and ankles. It begins between the fingers and on the thenar eminence as a pink papular eruption on an erythematous background. As it spreads over the wrists and forearms the papules become confluent. Desquamation is the rule, and if it is severe it may lead to exfoliation. The irritation is so intense that removal from contact is essential.

A great number of workers show minor degrees of cyanosis, with little or no pallor. Very often the condition is symptomless. Occasionally a worker who looks quite purple declares that he has never felt better in his life. The more serious cases present the TNT facies, a condition brought about by the combined effects of methaemoglobinaemia and vasomotor changes. It has been described by Moore (1918) and Roberts (1941). There is slight pallor, but the striking change is a lilac cyanosis of the lips, tongue, lobes of the ears, and curve of the helix. The appearance is so difficult to detect in artificial light that inspection of night-shifts is valueless. It is lessened by excitement or by mild exercise, and for this reason it is best detected by the medical officer when in the department during work rather than on a medical parade. Some of these cases develop symptoms such as breathlessness on exertion, lassitude, and a tightness behind the sternum.

Toxic gastritis is a definite syndrome. The patient is weary and miserable and has a heavy ache in the epigastrium together with loss of appetite. The patient is constipated, has nausea and vomiting which may be unrelated to food, looks ill, worried, and wretched, and may show the TNT facies. In the cases falling into this group Lane (1942) found the liver enlarged and tender. Investigations disclosed little. The laevulose tolerance test was usually normal, barium and fractional test meals showed no abnormality, and blood examination was normal. The urinary coproporphyrin, however, was raised in over half the cases.

The patient must be removed to hospital. A thorough bath is followed by scrubbing of hands, fingers, feet, and toes with ether until no pink reaction is obtained with alkaline alcohol. The nails should be closely cut. The bowels should be moved as soon as possible and kept open. A bland diet is allowed as soon as it can be tolerated. Fluids are given in large quantities with as much fresh fruit and vegetables as can be obtained. These cases usually clear up so far as the major symptoms are concerned after a few days' rest in bed. In a few of the worst cases it has taken two or three weeks before the patients have been sufficiently free from symptoms to get up. In nearly all cases, however, the fatigue has persisted and it is almost always the last symptom to disappear. Cases of this sort should never be allowed to return to contact.

Toxic jaundice is a rare complication, but it has a mortality of 30 per cent., so it must be treated seriously. If cyanosis occurs in one in 10 of the workers jaundice attacks one in 500. The greatest incidence of jaundice is in the third month of employment. Sometimes a latent interval occurs between removal from exposure and the onset of jaundice; thus, a woman who left work owing to an injury developed jaundice five weeks later (Panton, 1917). Premonitory symptoms such as drowsiness, giddiness, depression, and dark urine are sometimes present or the attack may be heralded by cyanosis or toxic gastritis. But it may arise without warning, and some patients even maintain that they feel perfectly well. The intensity of the jaundice varies; the stools are light coloured and the urine dark. The liver is palpable at some stage of the illness in most of the cases. Sometimes it is soft and tender in the early stages, but it usually becomes firm and non-tender at the end of the illness. The serum bilirubin figure may rise as high as 15 mg. per 100 c.c. The laevulose tolerance test is of little help, and the lack of a simple yet comprehensive test of liver function is a great disadvantage. The one investigation which shows a definite abnormality is the urinary coproporphyrin (Rimington and Goldblatt, 1940). In two fatal cases described by Lane in 1942, the figure was some 50 times greater than normal. The estimation was carried out some weeks before death and is, therefore, a striking finding. The prognosis is always uncertain, but grave symptoms of hepatic insufficiency sometimes appear rapidly. The morbid appearances are those of yellow and red necrosis of the liver with great reduction in its size and weight. The necrosis of the liver cells may be associated with infiltration and subsequent fibrosis resembling ordinary portal cirrhosis. There is little attempt at regeneration (Turnbull, 1917). However, typical multiple nodular hyperplasia of the liver has been described in a TNT worker who died of aplastic anaemia four months after her attack of toxic jaundice (Davie, 1942).

Aplastic anaemia sometimes occurs among TNT workers, but its incidence is very small. In 1917 Panton investigated 34 cases of sickness arising among workers in TNT. Of these, 28 had toxic jaundice, six had aplastic anaemia, and four had gastritis. Toxic jaundice and anaemia appeared to be separate pathological states. Anaemia might occur without jaundice and only about

17 per cent. of the jaundiced patients became anaemic. The latency of the blood changes was even longer than the latency of the jaundice, for it was found that anaemia could develop as long as nine months after exposure to TNT had ceased. The anaemia was always fatal. Lane (1942) described three cases of aplastic anaemia, all in men. Each case presented a profound normocytic anaemia associated with agranulocytosis and a low platelet count, all the blood-forming elements being affected. Liver and nucleotide therapy was attempted without improvement, the only measure which met with any success being repeated blood transfusions. In this way, one of the patients was kept alive for some months until his marrow began to regenerate. When examined nine months after the beginning of his illness, and four months after his last transfusion, this man had retained his red-cell count at the same level and his haemoglobin had increased by 20 per cent. His white-cell count remained in the neighbourhood of 6,000 per c.mm., with a normal differential count, and his platelets also had returned to normal. He still had an enlarged liver and his spleen had become palpable. In two cases of TNT aplastic anaemia, Turnbull (1917) found at necropsy fatty marrow throughout all the bones. In each case the liver was rusty-brown from an excess of iron pigment, and multiple petechial haemorrhages were present in the tissues.

There seems to be some evidence, as in the case of benzene, that an early effect of TNT may be to stimulate the bone-marrow. Thus Davie (1942) described a necropsy on a woman TNT worker who showed acute toxic purpura and died at home without any haematological examination prior to death. At necropsy she presented the features of purpura haemorrhagica. No anaemia was apparent, but the liver showed very early acute necrosis. Her marrow was markedly hyperplastic, the femur containing red marrow throughout the upper three-quarters of its length, and microscopically all the elements of the marrow were represented.

Stewart (1943) examined a number of students who had volunteered to fill shells with TNT during their vacation. Their chief subjective complaints were nausea with variable loss of appetite, diffuse abdominal pain, vomiting and diarrhoea, fatigue, and nasal and throat irritation. The symptoms came on after an initial period when there was an increased sense of well-being accompanied by a voracious appetite. There was evidence of haemolysis in over 85 per cent. of the students, with a fall in haemoglobin, red cell, and haematocrit readings. There was also an increase in reticulocytes, bilirubinaemia with urobilinuria, and a marked erythroblastic response in the marrow. The reticulocyte response was not maximal until a few days after exposure had ceased. This suggests that TNT, in addition to a destructive action on the circulating red cells, also affects the bone-marrow.

Experience in industry goes to show that when a poison is absorbed through the skin the application of effective measures of prevention is most difficult. In 1917 Legge minimized the risk of TNT poisoning, not by any single precaution, but by the combination of several, of which alternation of

employment, periodical medical examination, ventilation, and clean working conditions were the chief. Success was not achieved until mechanical means were substituted for the hand carriage of shells, combined with measures of cleanliness which were so precise as to prevent the contamination of the outside of the shells by TNT.

Unfortunately, in 1939, hand contact again became widespread. In filling factories TNT is used either molten, powdered, or in pellets known as biscuit. In the preparation of *amatol* and *baratol*, in filling shells, bombs, and mines, and in the breaking of biscuit, both contact with the skin and the production of dust are inevitable. In these processes further dangers are involved because solid TNT is spilled on the benches and it adheres to stemming rods, pouring cans, and funnels. Also, the cleaning of these tools and the shops themselves, unless done properly and under supervision, very often entails worse contact than the filling itself (Swanston, 1942). Fume hazard occurs where TNT is melted and where shells and anti-tank mines are filled. In ill-ventilated shops with dust and fume constantly present in the air, a certain amount of TNT must be inhaled and ingested.

In 1942, Himsworth and Glynn made experimental observations which suggest that a high fat diet renders rats more susceptible to TNT poisoning. It seems advisable, therefore, to arrange for TNT workers a diet of high protein and carbohydrate content with low fat.

Between 1916 and the end of 1941, 475 cases of TNT poisoning were notified. Of these, 125, or 26.3 per cent., ended fatally. In many factories to-day the conditions need to be improved by better ventilation, especially local dust extraction, and by the provision of better tools and the introduction of machine filling. Washing facilities must be extended and the supply of protective clothing improved. There should be a stricter supervision of the workers by people who are sufficiently intelligent and interested to appreciate the dangers of the work and the methods by which they can be avoided. Workers and supervisors must be trained to the job and penalized if rules are not obeyed.

Bridge (1942) summarizes the principles for the prevention of TNT illness as cleanliness of the air breathed, secured by effective ventilation or, if that is impossible, filtration through an effective respirator; cleanliness of the implements used and the cleanliness of the person, secured by protective clothing and by personal attention to the skin.

Dinitrophenol. Of all the dinitrophenols it is only the 2-4 isomer which has toxic properties. It is a pale yellow crystalline powder used as an explosive, in the dye industry, and for the preservation of timber. Mixed with picric acid it forms the French explosive *mélinite*. In France it was handled extensively in shell-filling factories during 1915 and 1916, and many cases of poisoning occurred, including 27 deaths. Absorption may take place through the respiratory tract, the alimentary canal, and the skin. Heat aids absorption and therefore more cases of poisoning occur in the warm days of summer. Alcohol influences the development of toxic phenomena in

man; cases of poisoning are more numerous the day after a holiday and among alcoholics.

Workers show yellow staining of the face, legs, and forearms, and especially the palms and soles. Mild poisoning is characterized by lassitude, slight headache, night sweats, and fatigue on the least exertion. Workmen may lose weight from the time they first take up the work. Acute intoxication comes on suddenly with a sensation of extreme weariness in the limbs and painful constriction in the chest, a burning thirst, abundant sweats, and an agitation and anxiety which is characteristic. Other signs are pallor, with slight lilac cyanosis of the lips, dyspnoea, and scanty urine which may be a deep orange colour owing to the presence of aminonitrophenol. In more severe cases death may take place in a few hours after a rise of temperature to 104° F. or over. The victim has severe sweating, intense thirst, and sometimes colic and diarrhoea. The state of anxious terror and restlessness is typical, and is followed by coma, convulsions, and death. Temperatures as high as 109.4° F. have been recorded and in some cases there was a rise of several degrees after death (Perkins, 1919). Necropsy reveals no characteristic lesions. When the dose is not fatal the symptoms rapidly improve and many workers develop a tolerance to the poison (Martin, 1930).

In 1918, when it became necessary in Great Britain to use dinitrophenol, the manufacturers profited by the experience in France and took extensive precautions. The men employed were provided with underclothes and overalls into which they changed from their ordinary clothes, a separate cubicle being provided for each man. The washing and bathroom facilities were all that could be desired. Exhaust ventilation was applied locally to remove the fume in melting the compound and also in filling the shells. Dust which collected round the margin of the shell was removed by a vacuum cleaner. As a result of these measures, combined with daily examination of the urine, little or no trouble has occurred from handling dinitrophenol in Great Britain (Legge, 1934).

The mode of action of the dinitrophenols has been investigated by experiment. It was discovered in 1885 that certain nitrophenols possess marked influence on metabolism (Cazeneuve and Lépine). In 1929 this work was amplified by Heymans and Bouckaert, who showed that nitrophenols not only cause a great increase in oxygen consumption, but if the administration be pushed there is also a rise in temperature terminating in a fatal hyperpyrexia. In 1933 Cutting, Mehrtens, and Tainter used 2-4 dinitrophenol in the treatment of obesity. The compound, administered to patients in doses of 3 mg. per kg. of body weight, caused a rise in basal metabolic rate and loss of weight, unattended by tachycardia. The treatment became very popular and, within a year, some 100,000 persons in the U.S.A. had used this substance for obesity. Proprietary preparations appeared under various names, such as *aldinol*, *dekryls*, *dinitronal*, *dinitrolac*, *dinitrolc*, *dinitrosc*, *dinitrovo*, *nitraphen*, *nitrobase*, *nitromet*, *reduzols*, *slendite*, and *slim*. Toxic symptoms were soon reported including urticaria, exfoliative dermatitis

(Hitch and Schwartz, 1936), jaundice (Sidel, 1934), neutropenia (Davidson and Shapiro, 1934), fatal agranulocytosis (Silver, 1934), peripheral neuritis (Nadler, 1935), and loss of the power to discriminate between sweet and salt tastes (Tainter, Stockton, and Cutting, 1933). The literature was reviewed by Hardgrove and Stern (1938). Albuminuria, cloudy swelling of the renal tubules, fall in blood-pressure, electrocardiographic changes, fullness in the ears, deafness, and decrease of sugar tolerance have also been described.

After dinitrophenol had been in use for four years cataract was found to be a late complication of the use of the drug. The shortest time reported before its appearance was three months, and the longest 18 months. The smallest total amount of dinitrophenol taken in these cases was 9 gm. and the largest 123.5 gm. The change is bilateral and the lens fibres alter so quickly that the cataract swiftly progresses to total blindness (Horner, Jones, and Boardman, 1935). No case has shown spontaneous resolution and most have progressed to complete opacity within about three months. By 1936, more than 60 cases of cataract had been published in the United States of America. This final disastrous effect of dinitrophenol, together with the fact that it could be obtained only by a physician's prescription in most countries, brought to a close the unfortunate popularity of this drug. Deaths have been rare and where they have occurred the dinitrophenol has been excessive, for example 10 mg. per kg. of body-weight, repeated for four or five days (Poole and Haining, 1934).

Aniline. Aniline is a colourless oily liquid, with a distinctive aromatic odour. It turns brown on exposure to air and light. It is handled in the manufacture of dyes, explosives, perfumes, pharmaceutical products, and photographic chemicals. It is used in dyeing, calico painting, painting, varnishing, and rubber processing.

The high lipid solvent power of aniline leads to its ready absorption through the intact skin. Experience has shown that in factories most of the serious cases of acute poisoning occur when the workers have had their clothing or skin soiled by aniline. Its absorption by the respiratory tract also occurs, especially after the breaking of vessels containing aniline, or where a workman enters a chamber filled with the vapour. Danger from aniline vapour is much greater during hot weather. At these times, when the work is over, numerous cases are observed of headache and slight cyanosis.

Many homologues of aniline, especially the *nitro*-anilines, are absorbed through the skin, and those which are sufficiently volatile are dangerous if inhaled. *Para*-nitraniline seems to be considerably more poisonous than aniline. In the absence of efficient locally applied exhaust ventilation this substance must not be packed in powder form for fear it should produce systemic symptoms, dermatitis, or conjunctivitis. The aniline sulphonic acids are harmless.

In a mild case of aniline poisoning the face flushes, the man experiences a sense of fullness and throbbing in the head, burning in the throat,

tightness in the chest, and then violent headache with dizziness and noises in the ears. The flushed face becomes bluish-grey, and the nose, ears, lips, tongue, and nails turn lilac. There is a sensation of weakness in the knees, and a staggering gait. If the man is promptly removed from all contact with aniline, recovery is rapid and the cyanosis disappears within the 24 hours. This disappearance is more rapid than in poisoning by *nitro*-derivatives of the aromatic series, probably because aniline becomes changed more quickly into hydroxylated products capable of being eliminated in the urine (Engel, 1930).

The recording spectrophotometer gives an exact picture of what happens to the methaemoglobin in the blood in these circumstances. Hamblin and Mangelsdorff (1938) recorded the case of a man who disregarded instructions and wore leather shoes which became contaminated with aniline oil while he was cleaning up the liquid spilled from a tank. He worked at this job for about four hours and then reported sick, complaining of severe headache, dizziness, weakness, and aching all over. He showed deep bluish-grey cyanosis, his pulse was 112, and his respiration 22. A curve of his venous blood plotted on the recording spectrophotometer showed 61 per cent. of methaemoglobin. This curve, repeated two hours later, showed a drop to 59 per cent. After resting quietly for four hours, the patient still had severe headache and was deeply cyanosed. However, his pulse had dropped to 80 and he was less lethargic. A blood curve at this time showed 34 per cent. of methaemoglobin. The following morning he felt well, had no headache, and his colour was normal. The blood curve then showed 5 per cent. of methaemoglobin. The following day the patient remained well, and the curve showed 3 per cent. of methaemoglobin.

Punctate basophilia is a valuable early sign of aniline poisoning. In 1907 Malden investigated the cases of 13 men employed in aniline black dyeing. There was so much aniline vapour in the atmosphere in which they worked that all unpainted deal woodwork was stained bright yellow. Of the 13 men, none had been employed for less than one year and all had suffered at some time or other from symptoms of aniline poisoning. The blood in six of the 13 men showed punctate basophilia. The number of cells affected varied from two or three in the whole film in the slight cases to 10 or 12 in every field of the microscope in the more pronounced cases. These observations have often been confirmed. Thus, Agasse-Lafont, Feil, and de Balsac (1926) found fine basophilic granules in the red cells of one-third of a series of men exposed to aniline.

In more severe cases, the colour of the face is a deep bluish-grey, and the lips and tongue are livid or almost black. The victim trembles and staggers, and complains of weakness in the knees. These symptoms may be followed by nausea, vomiting, and cramps in the abdomen. Extreme weakness comes on and sometimes a few hours after the onset of the attack consciousness is lost. The respiration is shallow and quick, the pulse small, rapid, and irregular, the skin is cold, and the blood-pressure drops. If coma persists

the respiration and pulse grow progressively slower. There is involuntary defaecation and micturition, and convulsions usually come on just before death. It is a characteristic feature that the attack seldom takes place while the man is at work, but almost always while he is on his way home or even some hours later (Hamilton, 1925). In serious poisoning, the blood turns brown and may even be the colour of chocolate. The urine is either dark brown or the colour of port wine because it contains haemoglobin and methaemoglobin. Quite often in the first days of the poisoning strangury occurs and the urine then contains red blood-cells.

Prolonged absorption of small quantities of aniline leads to chronic poisoning. In such cases cyanosis does not persist after the patient leaves his daily work, but he shows the weakness, fatigue, and slight giddiness and dyspnoea of anaemia. The blood shows a mild low colour-index anaemia, sometimes with polychromatophilia and punctate basophilia.

The manufacture of nitrobenzene and the reduction of nitrobenzene and nitrotoluene to aniline and toluidine must take place in closed vessels. The escape of small quantities of aniline into the atmosphere is very difficult to prevent, and so ample ventilation must be provided. In addition to the technical regulations, there must be insistence on cleanliness of the work-rooms, personal cleanliness on the part of the workers, and provision of baths and changes of clothing. Contact with aniline, especially on the skin, must be carefully avoided, and the spilling and splashing of the liquid forbidden. All workers must be instructed as to the symptoms of aniline poisoning and the steps to take should it occur. Regular medical inspection of workmen is desirable.

Workers, especially those newly employed, must be under supervision in order that help may be given on the first sign of poisoning. Medical assistance should be within easy reach. Systematic instruction should be given in first-aid methods and the use of apparatus for oxygen and carbon dioxide inhalation. The possibility of skin absorption must always be borne in mind. A victim whose skin or clothing has been splashed with aniline may turn blue in the face and begin to stagger. Someone may take him out to the fresh air or administer oxygen, when what he most needs is to have his clothes removed and be given a bath. Workers entering stills and similar chambers should always be equipped with breathing apparatus and a supply of oxygen. Other aids, such as safety belts which are held by helpers, involve certain risks, especially as the rescuer is easily induced to spring to the assistance of his unfortunate mate without the necessary breathing equipment. The frequency of such accidents calls urgently for the provision of breathing apparatus.

Workers employed in the manufacture of synthetic dyes sometimes suffer from papillomata of the bladder, which may become malignant. It is unfortunate that the name *aniline cancer* was given to this disease, for subsequent work has shown that other aromatic amines and especially β -naphthylamine may be responsible. The first cases were recorded by Rehn in 1895.

At that date the commercial preparation of aniline dyes had been established for some 30 years and had become a flourishing industry, especially in Germany. Rehn discovered three cases of bladder tumour among a group of 45 men who were engaged in the preparation of fuchsine, and suggested that the condition followed a chronic irritation of the mucous membrane of the bladder by certain chemical compounds excreted in the urine over a period of many years. In 1912 Leuenberger published 18 similar cases from Basle and offered valuable statistical evidence showing that the incidence of this disease was 33 times greater among dye-workers than among the remainder of the male population. Curschmann in 1920 undertook a systematic inquiry into all traceable cases of aniline cancer from German dye factories up to that date and was able to collect 177 cases. In the manufacture of synthetic dyes in Great Britain about 40 fatal cases have been recorded. Similar observations have been made in the United States of America, Russia, Austria, and Italy. The total number of these occupational tumours so far put on record in the various countries is approximately 550, but this does not represent the total incidence (Hueper, 1938).

The manufacture of aniline dyes involves the use and production of many chemical substances. For a long time it was not known which substance attacks the bladder, but it seemed, by a process of exclusion, to be an *amino*- and not a *nitro*-compound. In 1926, Oppenheimer suggested the name *amino-tumour*. In course of time suspicion fell upon many substances including aniline, *para*-toluidine, xylidines, naphthylamines, fuchsine, benzdine, and rosaniline. The difficulties met with in trying to trace the substance responsible are typical of those found in the investigation of all complex industrial processes. In the dye industry it is common to have two distinct processes going on in the same room. Further, in the case of a disease with such a long latent period, the workman may have moved from one factory to another or from one department in the same factory to another, each change bringing new compounds into question. Lastly, the same compounds used in different processes may be attended with very different degrees of danger. Thus, in making benzdine, there may be greater exposure to aniline vapour than in the manufacture of aniline itself (Hamilton, 1925).

In 1938 Hueper, Wiley, and Wolfe succeeded in producing papillomatosis and carcinomatosis of the bladder in dogs by daily subcutaneous and oral treatment with β -naphthylamine. They used from 300 to 450 mg. of this substance daily for periods of 20 to 32 months. The lesions observed on cystoscopic and histological examination of the bladders of 12 of the 16 dogs thus treated were identical with those seen by these authors in cystoscopic and histological examinations of dye workers. The tumours continued to grow and to become more numerous in some of the dogs after the treatment had been discontinued. In one dog the first neoplasms in the bladder were noted several months after exposure had ceased. Metastatic deposits were

not found in necropsies performed upon the dogs, though in one case the carcinoma had invaded the subserosa of the bladder.

In dye workers the period of exposure is usually 12 years, but tumours have developed in men who had been in the industry from four to 27 years. A number of men may work together in a dye factory for 30 years under apparently identical conditions and, although bladder tumours may arise early in some and late in others, the majority remain unaffected. As to the route of absorption, the respiratory tract as well as the skin may be involved, for occasionally members of the clerical staff of dye factories have developed bladder tumours.

The patient first seeks advice because of haematuria which may be either intermittent or constant. Cystoscopy reveals either small haemorrhages in the trigone or multiple papillomata, sometimes benign, sometimes malignant. Macalpine (1929) pointed out that there is often a premonitory period in which the patient suffers from symptoms of cystitis such as frequency of micturition with strangury. He has found the cystoscopic picture to differ from that seen in septic cystitis in that the mucosa is more brightly red and shows a tendency to mottling. The morbid anatomy and histology of aniline tumours appear to be identical with that of other bladder tumours.

Curschmann (1920) observed that the incidence of bladder tumours diminished considerably in the Frankfurt district after the institution of various protective measures in the factories, such as general cleanliness in the workrooms, adequate exhaust ventilation for the removal of vapours, mechanical transport of chemical products in closed containers, and improvements in the personal hygiene of the workmen. Nevertheless, bladder tumours still occur in large numbers in the dye industry in various parts of the world.

Workers exposed should be told both of the risk they run and of the nature of the symptoms. Soon after the first cases were discovered in 1895 facilities were provided in the Höchst factories for cystoscopic examination of every suspicious case. Credit was due to the management for this step, and similar measures have now been instituted in dye works all over the world. The strongest argument for the routine use of the cystoscope in aniline dyeworks is that men have remained well for a number of years after cysto-diathermy of a papilloma. Early diagnosis of all cases would ensure removal of every papilloma before it did any harm.

Tetranitromethylaniline. *N*-nitro-*N*-methyl-2,4,6-trinitraniline, or tetranitromethylaniline, is the explosive *tetryl* or *tetralite*. It is known in the fighting services as *composition exploding* or *CE*. It is a pale yellow crystalline powder, very stable when pure, but it undergoes detonation readily and is frequently used as a primer in detonators.

Tetryl causes yellow staining of the hands of workers in one to three days and of the face, neck, scalp, and hair in one to three weeks. The colour deepens to orange on exposure to sunlight. New workers sometimes complain of a sharp tingling sensation in the nose. This causes sneezing and.

rarely, epistaxis. These symptoms are due to the irritating effect of the crystals on the nasal mucous membrane. The commonest complaint from *tetryl* workers is dermatitis. This starts as an erythema, followed by a pink papular eruption accompanied by some exfoliation. It generally affects the face first, especially at the sides of the nose, and around the eyes and the corners of the mouth. Later the condition spreads to the chin, neck, and back of the head, causing severe irritation. In some cases there is conjunctivitis and even gross oedema of the eyelids which may prevent the patient from opening the eyes for two or three days. Mild cases clear up in a few days, but in severe cases the rash often persists for two or three weeks. Suspension from work is seldom necessary. *Tetryl* rarely gives rise to any constitutional symptoms. A certain number of new workers complain of epigastric pain with nausea or vomiting. These symptoms bear no relation to food and are seldom severe enough to keep the patient away from work (Hilton and Swanston, 1941).

Protective clothing should be provided and it is necessary to insist upon frequent changes of underclothes. Work-rooms must be well ventilated and the atmosphere dry. Great care should be taken to avoid raising dust. The hands should be washed thoroughly in running water before the face is washed. The addition of five per cent. sodium sulphite will assist removal of *tetryl* by converting it into a soluble substance (Silver, 1938). Workers should be warned against the use of proprietary ointments. A water-soluble skin varnish can be used on the face and arms before beginning work. Calamine lotion should be applied. Oils and ointments aggravate the condition and must be avoided except after the acute inflammation has subsided, when the affected parts may be cleansed with olive oil. Workers who recover from an acute attack in less than a fortnight may be allowed to resume contact work after a further week. If a second or third attack occurs it is an indication that the patient is susceptible and should be removed permanently from handling *tetryl*. A worker who develops oedema of the face and peri-orbital tissues is a bad risk and must be removed permanently from contact at the first outbreak of the eruption.

Phenylenediamine. Of the three isomers of phenylenediamine the *ortho*-compound is of little importance. The dye *ursol* as used in the fur industry is a mixture of the *meta*- and *para*-isomers. *Para*-phenylenediamine is a colourless crystalline solid which rapidly oxidizes in the air, darkening in colour. It is used in dilute aqueous solution as a constituent of hair dyes, including proprietary preparations such as *inecto*, *koorpa*, and *primal*.

It is well known that this dye may cause dermatitis and sometimes asthma. In 1929 Mayer and Förster examined 181 persons employed in the fur trade in which *para*-phenylenediamine was used as a dye and found that 111 had suffered from dermatitis or asthma. It seems that the asthma is due to direct stimulation of the bronchi rather than to allergy, since Hanzlik (1923) was able to demonstrate constriction of the intact bronchi of dogs and guinea-pigs.

The skin eruption is an eezematous dermatitis appearing as minute pink papules on the face, neck, and forearms. Moist points, such as the lips, corners of the mouth, angles of the eyelids, and orifices of the nose especially suffer (White, 1924). In discussions of the aetiology of fur dermatitis many authors dismiss personal idiosyncrasy as irrelevant. However, Ingram (1932) demonstrated delayed reactions to patch tests and claimed that the dermatitis must therefore be a sensitization phenomenon. The tests were made with pieces of lint saturated with one per cent. aqueous solution of *para*-phenylenediamine. Approximately four per cent. of 1,000 normal subjects showed dermatitis which appeared from 24 hours to 24 days after the test was applied.

The systemic effects of *para*-phenylenediamine are less common and have received little attention. Nott (1924) described a case of systemic poisoning without dermatitis in the proprietor of a hairdressing saloon. This patient had suffered for three years from attacks of weakness and vomiting sometimes followed by unconsciousness. After a night's rest the effects disappeared. He was seen in a severe attack, when his face was cyanotic and swollen. The lips were violet, the tongue swollen, and the gums purple. After three months' avoidance of exposure to the dye he had no further symptoms.

Israëls and Susman (1934) recorded the death of a girl aged 21 years who for five years had worked in a hairdressing department as a dyer. She used *para*-phenylenediamine and was provided with rubber gloves, but after she had applied the dye she had to shampoo the hair, and for this the gloves were removed. At no time had she experienced any skin reaction directly traceable to the dye. She developed toxic jaundice and died of hepatic insufficiency after an illness lasting seven months. At necropsy the liver was small and showed the changes of subacute atrophy with regeneration nodules. The patient was evidently unusually susceptible to the poison.

Baldrige showed in 1935 that anaemia may follow the use of *para*-phenylenediamine as a hair dye. At least four cases have been described and in all of them the anaemia was of the macrocytic, high colour-index type, and refractory to treatment with iron or liver. One of these women repeatedly showed a red-cell count below 1,000,000 per c.mm., and though she improved temporarily after eight blood transfusions her condition remained unchanged four years after the onset of symptoms (Bomford and Rhoads, 1941).

The use of *para*-phenylenediamine for cosmetic purposes and as a dye for furs, stockings, and blouses might with advantage be forbidden. Short of this, care must be taken to remove surplus *para*-phenylenediamine from dyed fabrics by thorough washing. The workers who dry or cut fur must be protected from dust containing the dye, and where those exposed to risk are men they should be clean shaven. Hairdressers handling the dye must wear rubber gloves.

Tri-ortho-cresyl phosphate. Tri-ortho-cresyl phosphate, known in industry as *lindol*, is used in the recovery of phenol residues from gas plant effluents

and also as a plasticizer in the plastics industry. A plasticizer is a substance used to render a plastic material more pliable. By alteration of the amount of the plasticizer added such characteristics as flexibility, hardness, water-resistance, and inflammability can be varied between quite wide limits. Pure tri-*ortho*-cresyl phosphate is a crystalline solid. The product used in industry is a liquid owing to the presence of the other isomerides. Tri-cresyl phosphate is prepared by treating cresols with phosphorus oxychloride in the presence of an aluminium catalyst. It has been the boast of industry in the United States of America that in a plant manufacturing 100,000 lb. of this material a day without any special precautions no cases of poisoning have occurred.

Since 1939 black-out conditions in this country have led to a less fortunate state of affairs, and three workmen employed in a manufacturing plant have developed polyneuritis (Hunter, Perry, and Evans, 1944). All three men worked in a room about 25 ft. long, 12 ft. wide, and 12 ft. high which, owing to black-out regulations, was totally enclosed during the hours of darkness, although it was provided with a roof vent. During the day-time doors and windows were open. The men worked at wash tanks which were roughly cubic vessels of about 5 feet side, with a partially open top. The closed-in portion of the top supported the various fittings, one of these being a 6-inch vent pipe extending through the roof to the open air. Crude tri-cresyl phosphate entered these tanks at a temperature of approximately 60° C. At this stage it contained hydrochloric acid which gave it an unpleasant irritating odour. However, it was immediately cooled down by treatment with an equal volume of cold water, this operation being carried out by opening a valve and shutting it at the appropriate moment. The washing was automatic, but it was nevertheless possible for the men to inhale vapour from the tanks. The cold tri-cresyl phosphate is of low volatility, having a very small vapour pressure at ordinary temperatures. The *ortho*-isomer content of the finished product was about 60 per cent. The three afflicted men also handled tri-phenyl phosphate, but there is good reason to believe that this is non-toxic. Experimental evidence will be quoted later which strongly suggests that the phenyl ester and also the *meta*- and *para*-cresyl esters are harmless.

The clinical picture of tri-*ortho*-cresyl phosphate poisoning is that of a polyneuritis with flaccid paralysis of the distal muscles of the upper and lower extremities. Slow but complete recovery usually occurs. Opportunities to study this clinical picture occurred during a period of 40 years prior to the discovery of the first victim of industrial poisoning. It was encountered in patients treated for pulmonary tuberculosis with phospho-cresote, in people who had partaken of a beverage known as *Jamaica ginger* or *jake*, in women who had taken apiol as an abortifacient, and in certain victims fed on a soya bean cooking oil adulterated by accident.

In 1899 Lorot reported six cases of multiple neuritis out of 41 cases of pulmonary tuberculosis treated with phospho-cresote. This substance was

discovered in 1894. Later it was shown to contain 15 per cent. of tri-*ortho*-cresyl phosphate. In the next 35 years 53 additional cases were recorded in various parts of Continental Europe (Roger and Recordier, 1934).

In the spring of 1930 there appeared suddenly, in the mid-western and south-western states of the United States of America, an outbreak of paralysis characterized by bilateral foot- and wrist-drop. During March and April of that year almost 4,000 cases were reported in the press throughout the United States of America. During the whole year 15,000 people were affected and of these 10 died. A connexion was immediately recognized between this paralysis and the ingestion of adulterated samples of a popular alcoholic drink known as *Jamaica ginger* or *jake*. The quantity of ginger fluid consumed was not the determining factor in the severity of the symptoms which followed; a single drink is known to have produced the same result as that following the use of the beverage for many days.

The clinical picture develops by three stages. In some cases there are early transient gastro-intestinal symptoms including nausea, vomiting, diarrhoea, and abdominal pain. These clear up and a symptom-free interval follows lasting from five to 21 days, the average being 10 days. This interval is followed by soreness of the muscles below the knees and numbness of the toes and fingers lasting several days and followed by weakness of the toes and bi-lateral foot-drop. After another interval of about 10 days weakness of the fingers and wrist-drop follow. This paralysis is not usually as severe as that in the feet and legs. In the upper extremities paralysis does not extend above the elbows. The thigh muscles may be involved in advanced cases. There are neither sensory changes nor loss of sphincter control.

By July, 1930, Smith and Elvove proved that the adulterated beverage contained about two per cent. of tri-*ortho*-cresyl phosphate and that this caused the paralysis. The reason for including this substance as one of the ingredients will probably never be known. It may have been used on account of its physical properties. By subcutaneous injection of samples of the adulterated drink, as well as of pure synthetic tri-*ortho*-cresyl phosphate, Smith and Elvove succeeded in producing a paralysis comparable to that seen in human beings in a variety of laboratory animals including hens, rabbits, calves, dogs, and monkeys. Later in 1930 Smith and Elvove showed that the specific attack of tri-*ortho*-cresyl phosphate on the motor nerves is not shared by the *meta*- or *para*-cresyl esters nor by the phenyl ester. The minimum lethal dose of tri-*ortho*-cresyl phosphate was approximately 30 times less than that of tri-phenyl phosphate.

Zeligs (1938) had the opportunity to follow up 316 cases of *jake* paralysis during six years. His description of the clinical picture in 1930 and later in 1936 shows that the poison may attack the anterior horn cells and the pyramidal tracts, in addition to the peripheral motor nerves. In 1930 all the patients had typical foot-drop, the degree of paralysis varying from slight muscular weakness to complete flaccid paralysis of all the muscles of

the feet and legs. In about three-fourths of the cases the upper extremities became similarly involved, wrist-drop being common. The ankle-jerks were absent, the knee-jerks present and in many cases overactive. There were no abnormal plantar responses and no ankle clonus. Sensory changes were absent. During the next six years many of the patients recovered completely and others improved sufficiently to be able to use their hands and feet adequately. Out of 316 patients admitted to the Cincinnati General Hospital in 1930 a group of 60 were found still in institutions in 1936. They hobbled about with the aid of sticks. Physical examination showed spastic paralysis with adductor spasm, paralytic talipes, exaggerated tendon reflexes, and extensor plantar responses. In the upper extremities there was marked atrophy of the extensors of the wrists and of the interossei, with bilateral claw hands.

The initial conception of tri-*ortho*-cresyl phosphate poisoning as being a peripheral neuritis is therefore no longer tenable. The anterior horn cells and pyramidal tracts may sometimes be affected too, but the extreme muscular wasting tends to mask the involvement of the upper motor neurone. When muscular activity is partially restored the spastic signs of the previously hidden upper motor neurone lesion become clinically apparent. In such cases the end result resembles amyotrophic lateral sclerosis.

In 1931 ter Braak reported in Holland an outbreak of some 40 cases of paralysis from the use of apiol as an abortifacient. During 1931 and 1932 50 more cases were published from Germany, France, Switzerland, and Jugoslavia. Samples of apiol were found to be adulterated with tri-*ortho*-cresyl phosphate to the extent of 28 to 50 per cent. (Germon, 1932). Nobody knows why this substance was chosen as an adulterant. Neither in colour, taste, nor odour do the two oils resemble each other. In the women affected there was a lower motor neurone paralysis of the distal muscles of the extremities, without sensory loss.

In April, 1937, there occurred an outbreak affecting 68 people who had partaken of soya bean oil used for salads and for cooking. Forty-one of these people lived in Natal and the other 27 travelled in a ship which had been provisioned in Durban (Sampson, 1938, 1942). This oil was found to contain 0.4 per cent. of tri-*ortho*-cresyl phosphate. The victims first had gastro-intestinal symptoms and seven to 14 days later developed cramps in the calves of their legs. Ultimately lower motor neurone paralysis of the feet and hands supervened, but sensation was unimpaired.

Cases of tri-*ortho*-cresyl phosphate poisoning have recently occurred in Münster owing to shortage of fats in Germany. The patients were factory workers who had obtained a fat substitute from their place of work. They had taken it home and, because of the shortage of natural animal and vegetable fats, had used it to fry potato pancakes. They developed nausea, vomiting, abdominal cramps, and diarrhoea, followed in 10 days by rapidly increasing weakness of the feet, legs, and then arms. There was progressive atrophy of the muscles. As a result of this outbreak, a warning was issued

to factory medical officers in Germany, who were instructed to prevent recurrences by education and propaganda (Humpe, 1942).

Two of our cases recovered completely in periods of 10 and 12 months respectively. The third is still making slow progress, but is not entirely well at the time of writing, which is two years after the onset of symptoms. In order to try to prevent further harm, the firm employing the men fitted the wash-tank room with ventilators and a fan. The tanks were closed in and the vents fitted with injectors, so that the vapours might be quickly transferred to the open air.

Workers should be protected from contact or inhalation where tri-cresyl phosphate is manufactured and handled. It seems clear that the *ortho*-isomer is the dangerous one, but even the *para*- and *meta*-isomers cannot be considered innocuous for industrial use owing to the probability that the *ortho*-compound will be present with them. Equally it would be wise to regard tri-phenyl phosphate as potentially toxic until more evidence as to its action is available. The workmen should be provided with rubber boots and gloves. All tanks should be closed, and the work-rooms fitted with ventilators and fans.

Hamilton (1934) suggested that dangerous exposure to tri-*ortho*-cresyl phosphate might occur in the mixing of lacquers containing this material as a plasticizer, particularly if the ingredients were heated. There is no evidence that plastic materials containing tri-*ortho*-cresyl phosphate can cause poisoning from contact. Flinn (1943) was able to produce paralysis in chickens fed with *cellophane*, in amounts of 1 gm. per kilo. of body-weight, in 28 days. The *cellophane* contained 11 per cent. of tri-*ortho*-cresyl phosphate.

THE CHLORINATED HYDROCARBONS

The rapid growth of the moulded plastics and cellulose lacquer industries has led to the extensive use of many new solvents, most of which were little more than chemical curiosities before about 1925. Amongst these are the chlorinated hydrocarbons which have flooded the market, largely because the alkali industry requires an outlet for its by-product chlorine. The various members of the group are useful as refrigerants, as degreasers of metals, fire-extinguishers, cleansers of textiles, solvents for rubber, and thinners of cellulose lacquers. They are non-inflammable, non-combustible, and non-explosive, but they are far from harmless in their effects on the human body.

The action of carbon tetrachloride has been extensively studied because of its use in the treatment of hookworm disease. Tetrachlorethane dramatically attracted attention in England in 1914. A mass poisoning from leaking refrigerators in Chicago in 1929 led to an increase in knowledge of the action of methyl chloride. Trichlorethylene has been studied because of its extensive use in dry cleaning. It led to trouble in German industry in 1931. Chlorinated naphthalenes caused no serious harm until 1937.

The entrance of chlorine into an aliphatic hydrocarbon increases its toxicity, whereas the reverse is the case with an aromatic hydrocarbon. Thus chlorobenzene is less toxic than benzene and causes no trouble in industry. The toxic effects of the chlorinated hydrocarbons increase with their molecular weight, though this is compensated to some extent by a decrease in volatility. The effects of the *chloro*-compounds may be related to the activity of the halogen contained in them. Chlorine is certainly more active in the aliphatic than in the aromatic compounds. For instance, the *chloro*-derivatives of the paraffins are hydrolysed by boiling with aqueous alkali, whereas chlorobenzene is scarcely affected by this process. The *chloro*-derivatives of naphthalene hold an intermediate position between the aliphatic *chloro*-compounds and chlorobenzene, both as to stability and toxicity.

It is well known that at high temperatures and in an excess of air the halogenated hydrocarbons are decomposed. The decomposition products may contain free halogen, hydrogen halide, and carbonyl halide. As these gases are all highly toxic there is some risk to health where gas burners are present or welding processes are carried out in proximity to sources of the vapour of chlorinated hydrocarbons. As to smoking, it has often been asserted that phosgene is formed when trichlorethylene passes through burning tobacco. The work of Elkins and Levine (1939) throws doubt upon the danger of smoking in the presence of these vapours. They found that the extent of decomposition into the corresponding halide of trichlorethylene, dichlorobenzene, carbon tetrachloride, ethylene bromide, and ethyl bromide, occurring as a result of smoking cigars or cigarettes in the presence of their vapours, is of a low order and does not constitute a risk to health. It is essential that all illnesses occurring among workers exposed to the chlorinated hydrocarbons should be carefully recorded. Accurate case records are necessary in order to establish clear clinical pictures which can be readily recognized in the future. Only in this way can diagnosis be improved and workers' lives saved.

A large number of halogenated organic compounds are either definitely known to be liver poisons or are under suspicion. They include bromethol (avertin), carbon tetrachloride, chlorbutol (chloretone), chlorinated diphenyl, chlorinated naphthalene, chloroform, dichloromethane, ethyl chloride, ethylene dichloride, iodoform, methyl chloride, monoiodoethane, tetrachlorethane, and trichlorethylene. It is not suggested that all these substances are industrial poisons, but some of them are used in therapeutics as sedatives and anaesthetics and must be avoided in patients whose work exposes them to the chlorinated hydrocarbons.

Workers with a past history of jaundice, even mild infective hepatitis, or of any other liver disease, should not handle these substances, nor should workers with a past history of typhoid fever, malaria, gall-stones, or other diseases known to attack the liver. Workers receiving arsphenamine treatment for syphilis or those who are taking drugs believed to be injurious to the liver should not be further exposed in their work to potential liver

poisons. Neither should pregnant women be exposed to the chlorinated hydrocarbons because the liver in pregnancy is peculiarly susceptible to injury. Sedatives such as chloral hydrate and chlorbutol should be avoided, as also should the anaesthetics chloroform, trichlorethylene, bromethol (avertin), and ethyl chloride. No worker who has received such an anaesthetic should go back to his former occupation until after a long interval.

Where poisoning has actually occurred from exposure to a chlorinated hydrocarbon, alkaline glucose drinks together with large doses of calcium lactate up to 15 gm. a day should be given. Calcium gluconate may be given by intramuscular injection. The use of sugar and calcium salts is based upon the accidental discovery of Minot and Cutler (1929) that, though carbon tetrachloride causes a severe intoxication in dogs on a meat diet, the addition of calcium salts to such a diet produces a high degree of tolerance to the drug. The symptoms of poisoning are gastro-intestinal irritation and hyperexcitability followed by depression. There is retention of guanidine in the blood and hypoglycaemia. The relief and protection given by calcium salts seem to depend upon their antagonistic effect to the retained guanidine. These authors found that when calcium salts were administered to poisoned animals the nervous symptoms were relieved and the blood-sugar was restored to normal. However, if the blood-sugar was raised by the administration of glucose, the hyperexcitability persisted until calcium salts were given in addition.

Methyl chloride. Methyl chloride, or monochloromethane, is a colourless gas with a faint ethereal odour. It is used in the dye industry and in the preparation of chloroform. To an increasing extent it is replacing ammonia and sulphur dioxide in refrigeration. Its advantages for this purpose are its stability and low boiling point, and that it is non-corrosive to metals, relatively non-inflammable, non-explosive, and non-injurious to food, furs, or textiles.

The first cases of its poisonous action in industry were reported by Gerbis in 1914. The patients were two men working in a chemical plant, who suffered from nausea, vomiting, and extreme somnolence. The first patient slept for 24 hours with three interruptions for meals. The second patient was restless and ran excitedly about the factory doing everything the wrong way. He had dimness of vision which did not clear up for 14 days after leaving work. Subsequently, 41 cases were reported in Switzerland, Germany, and the United States of America, all of them being persons employed upon making, installing, or repairing refrigerators.

It is to Kegel, McNally, and Pope (1929) of Chicago, that we owe the fullest clinical description. Their paper is based upon 29 cases, many of them severe, with 10 deaths. In 1927 Baker described 21 milder cases amongst the employees of an American firm of refrigerator manufacturers and in 1930 a further 75 non-fatal cases. In Great Britain 10 cases were described between 1930 and 1935. A clinical account of seven further cases

was written by Jones in 1942. These occurred amongst a small number of travelling refrigerator repairers; six of the cases were of moderate severity and the seventh was the first severe case to be reported in this country.

In mild cases, exposure to the gas is followed by staggering gait, dizziness, and headache. Anorexia, nausea, and vomiting occur next day. The patient is rarely prevented from working.

In a case of moderate severity the patient is ill for several weeks. The staggering and dizziness are accompanied by drowsiness, malaise, and weakness. Ocular symptoms occur in about half of the cases, but their appearance is usually delayed for 24 hours. They include misty vision, diplopia, and difficulty in accommodation. Vomiting sometimes occurs for a week or more and diarrhoea has been described. Depression, diplopia, and misty vision have been known to persist for two months.

In more severe cases epileptiform convulsions occur and may lead to death. Involuntary movements include myoclonus and action tremors. Ptosis, strabismus, and diplopia are common, but optic atrophy does not occur. Slurred speech, amnesia, drowsiness by day, and delirium by night are occasionally seen. There is a rise of temperature, pulse, and respiratory rate. In the worst cases there is oliguria, occasionally with suppression lasting up to 48 hours. Fifty per cent. of cases have albumin and red cells in the urine. The detection of formic acid in the urine is not of diagnostic value, as was at one time thought. No case showed jaundice, though in necropsies fatty degeneration of the liver was seen. Anaemia occurs in some of the men affected, the red cells dropping as low as 3,100,000 per c.mm. and the haemoglobin as low as 50 per cent. Sometimes there is leucocytosis with a normal differential count. Sequelae such as ataxia, diplopia, misty vision, headache, drowsiness, and amnesia sometimes persist for as long as eight months.

Poisoning in refrigerator factories can be eliminated by exhaust ventilation. Unfortunately it is difficult to convince the refrigerator repairer that an almost inodorous non-irritating gas can be poisonous. He must be forbidden to stay in a room after he has heated liquid methyl chloride in the blocked evaporator of a refrigerator. The suggestion has been made that some pungent detector substance such as acrolein should be added in the proportion of one per cent. to the methyl chloride. The use of such a substance would draw attention to the dangerous nature of the gas, facilitate the education of those who handle it, and warn the householder of a leak from his refrigerator. Unfortunately it would afford no protection to infants, the infirm, or refrigerator repairers.

The discovery of safe refrigerants is progressing systematically. Chemists set out deliberately to discover a non-toxic, non-corrosive, non-inflammable, non-irritant refrigerant which would be safe to put in domestic refrigerators. It was found in dichlorodifluoromethane, known also by the trade name *freon*. Sayers, Yant, Chornyak, and Shoaf (1930) have shown that prolonged exposure of dogs, monkeys, and guinea-pigs to air containing 20 per cent. by

volume of dichlorodifluoromethane vapour does not lead to any ill effects. It is therefore probable that the use of this refrigerant involves little risk to the health of the worker.

Carbon tetrachloride. Carbon tetrachloride, or tetrachloromethane, is a colourless liquid with an odour somewhat resembling that of chloroform. It is used as a solvent in the rubber, chemical, pharmaceutical, and paint industries, as a cleansing agent in the dry cleaning industry, and as a constituent of fire extinguishers (*pyrene*), insecticide sprays, and soap solutions. It is used in machine shops and printing plants for the removal of grease, as a dry shampoo for hair, and as a household cleaning fluid under such trade names as *carbona* and *thawpit*.

In practice it is one of the least harmful of the chlorinated hydrocarbons. In animal experiments it has been shown to cause necrosis of the liver (Lamson, Robbins, and Ward, 1929). In man it may attack both liver and kidneys, but in most clinical histories so far published the symptoms of renal injury overshadow those of hepatic injury. The early stages of the illness are characterized by persistent headache, nausea, vomiting, diarrhoea, and tenderness over the liver, but such symptoms are often followed by oliguria, suppression of urine, and uraemia. Albumin, casts, and red blood-cells are sometimes found in the urine.

One of the earliest reported cases of carbon tetrachloride intoxication was that of a man who entered a reservoir, and later showed excitement and delirium followed by mild narcosis, with recovery in eight days (Lehmann, 1903). Deaths in industry from the anaesthetic effects of carbon tetrachloride are seldom encountered, though they have occurred from the use of this substance as a dry shampoo for the hair. Cases of chronic poisoning are not numerous, but are rapidly increasing. Boveri (1930) reported from Milan five cases in men preparing an insecticide which contained carbon tetrachloride. Two were poisoned severely, enlargement of the liver, albuminuria, and urinary casts being noted. Subsequently, profound diuresis occurred and both patients recovered.

Henggeler (1931) reported six cases of poisoning in one family in Switzerland. For three days they worked long hours cleaning and waxing the floors of a school. The wax, which contained carbon tetrachloride, was heated by the man and then applied hot by the entire family. All the patients suffered by the end of the third day from nausea, headache, and malaise. The man, who had undoubtedly breathed more of the vapour than the others, became dangerously ill and showed mental confusion, headache, hiccup, nausea, vomiting, diarrhoea, and scanty urine loaded with albumin. At the end of three weeks he was exhausted and emaciated, having lost 29 lb. in weight, but he gradually recovered after three months.

In 1932 McGuire reported from Boston seven cases of poisoning among workers passing felt through a warm mixture containing 33.3 per cent. of carbon tetrachloride to remove spots of grease. The symptoms were smarting

around the eyes and mouth, headache, nausea, vomiting, and diarrhoea, with acute nephritis in one case and jaundice with liver enlargement in two. All the patients recovered, the two with subacute necrosis of the liver remaining jaundiced for two months.

Dudley (1935) described two exposures to the vapour of carbon tetrachloride sprayed from *pyrene* fire extinguishers in confined spaces in British warships, and one exposure in a large, well ventilated work-room. Four men were poisoned in the first two exposures and were kept under observation in hospital. They all showed impairment of renal function, but they all recovered. One suffered from oliguria and jaundice, and 10 days after exposure developed convulsions. The blood-urea rose to 302 mg. per 100 c.c. and the patient was practically moribund when, on the thirteenth day, polyuria developed followed by recovery. Another man had almost complete anuria for 10 days, but no other symptoms of renal insufficiency and no jaundice. None of the 14 men who was exposed in the large work-room developed any untoward symptom or showed any impairment of renal function.

In some of the fatal cases following the use of fire extinguishers, oedema of the lungs has been found. It has been suggested that this is caused by the decomposition product phosgene, but it should be noted that oedema of the lungs has been found where there had been no contact of the carbon tetrachloride with any agents likely to bring about decomposition.

Simulation of an acute abdominal emergency has been recorded (Graham, 1938). The patient had been working with a dry cleaning apparatus which was leaking. Epigastric pain and vomiting were accompanied by oliguria and tenderness in the left loin. The pulse rose to 130 and the patient showed the Hippocratic facies with abdominal distension and tenderness. It was only the increasing tenderness in the loins and the blood-cells in a scanty urine which tipped the balance in favour of medical treatment rather than laparotomy. Witts, Stewart, and Kemp (1943) investigating a group of workmen exposed to carbon tetrachloride showed by means of opaque meals that there was hypermotility of the intestines associated with spasm.

Toxic amblyopia has been described by Wirtschafter (1933). All his patients already showed gastro-intestinal disturbances, and three out of five complained of blurring of vision and spots before the eyes. Examination by perimetry showed bilateral restriction of the colour fields. Wirtschafter suggested the routine use of perimetric examination of the visual fields of workers to detect intoxication at an early stage. Out of 93 men whose visual fields were examined Smyth, Smyth, and Carpenter (1936) found 10 with extensive and 16 with slight restriction, which was not closely correlated with the degree of exposure.

Cases of chronic slight intoxication have seldom been recorded. Amongst the symptoms in such cases are headache, nausea, loss of appetite, vomiting, loss of weight, nervousness, mental confusion, slight jaundice, and disturbances of vision. Dermatitis is mentioned by Davis (1934) and is regarded by him

as being due to the solvent action of carbon tetrachloride upon the fat in the skin.

In a series of cases exposed to risk, personal idiosyncrasy is striking. There may be little or no relation between the amount of exposure and the severity of symptoms. An occasional accident occurring in an enclosed space cannot be used as an argument against the employment of carbon tetrachloride as a fire extinguisher. The prompt use of this liquid has saved countless people from death by burning or asphyxia from the poisonous gases normally present in the smoke from fires; while on the other hand the victims of poisoning from the vapour of carbon tetrachloride, even those who are very ill, usually recover.

In treatment of cases acutely poisoned by exposure to the vapour in sufficient quantity to cause anaesthesia, it is important that the patient should not be placed upon the floor of the room where the accident occurred, for the vapour is five times denser than air and therefore accumulates on the floor.

Ethylene dichloride. Ethylene dichloride, or *sym.*-dichlorethane, is a colourless liquid with an odour like chloroform. It is used in industry as a solvent for oils, fats, waxes, resins, gums, and rubber, as an insecticide and fumigant especially for furs, in fire extinguishers, and in household cleaning fluids. Its toxicity after inhalation is not very high, ranking above trichlorethylene and slightly below carbon tetrachloride.

It is a powerful narcotic and was used as an anaesthetic by Simpson in 1848. In animal experiments Müller (1925) claimed to have produced fatty degeneration of the liver and kidneys, but no changes in the liver other than congestion and cloudy swelling have been recorded by other workers.

Hueper and Smith (1935) described a case in which death followed 22 hours after drinking 2 oz. of ethylene dichloride. The patient showed dizziness, increasing stupor, cyanosis, a rapid pulse, and heart failure. The urine contained albumin and sugar. At necropsy the kidneys showed extensive tubular necrosis with calcification resembling that seen in mercury perchloride poisoning. These authors suggested that this finding indicated excretion by the kidney of the substance itself or of a decomposition product, presumably oxalic acid. The liver showed fatty degeneration and, in addition, there was extensive haemorrhagic colitis. Ethylene dichloride is therefore capable of producing liver damage after inhalation, but its hepatotoxic action for man is less than that of tetrachlorethane or carbon tetrachloride.

Bridge (1933) recorded the case of a patient who suffered from acute symptoms after exposure to the vapour of ethylene dichloride. The man was fitting a coil in a glycol plant when he complained of vomiting, diarrhoea, giddiness, drowsiness, and slight breathlessness. In 1939 Wirtschafter and Schwartz reported three cases of ethylene dichloride poisoning which were due to exposure when cleaning yarn in a knitting factory. After four hours the men complained of dizziness, nausea, vomiting, epigastric pain,

weakness, and trembling. They were removed to hospital one hour later. In one case the liver was enlarged and tender. Leucocytosis was present in all cases, and liver damage was suggested by very low blood-sugar levels. All three patients showed a severe dermatitis of the hands which presented a raw scalded appearance. It was thought to be due to the solvent action of ethylene dichloride upon the fat in the skin. There was no evidence of kidney involvement. On admission to hospital the patients were given injections of 10 per cent. calcium gluconate with immediate relief of the epigastric pain and vomiting. All the patients recovered after one week and were discharged with instructions to take a high calcium, high carbohydrate diet.

Tetrachlorethane. Tetrachlorethane, or acetylene tetrachloride, is a colourless liquid with an odour resembling that of chloroform. At various times it has been sold under proprietary names such as *alanol*, *cellon*, *emaillet*, *novania*, *tetraline*, and *westron*. It is a good solvent for cellulose acetate which, being non-inflammable, is used for purposes for which cellulose nitrate (celluloid) is not adapted. Cellulose acetate dissolved in tetrachlorethane was used in 1914 as a waterproof coating for the wings of aeroplanes. On account of its toxic effects the use of this dope in the aircraft industry has become much restricted, in fact, forbidden in many countries. Tetrachlorethane is now used to make non-inflammable cinema film, artificial silk, safety glass, leather, and artificial pearls. It is also used as a dry-cleaning agent, as a solvent for lacquers, waxes, and resins, as a parasiticide, especially in hair washes for dogs, and as a fire extinguisher. It is used in the rubber industry, in the manufacture of gas-masks, tube cements, and floor waxes, and for the impregnation of furs and skins.

In 1911 Lehmann proved that tetrachlorethane is the most dangerous of all the chlorinated hydrocarbons, being about four times as toxic as chloroform and nine times as toxic as carbon tetrachloride. Three cases of poisoning after its ingestion have been recorded; the patients all became unconscious and died within 12 hours from central respiratory paralysis (Forbes, 1943). Complete narcosis can also occur when tetrachlorethane is absorbed through the skin (Schwander, 1936). In industry the normal route of absorption is through the respiratory tract. The clinical picture produced is that of toxic jaundice from necrosis of the liver.

In 1914 Jungfer reported the first cases of industrial poisoning from tetrachlorethane. They occurred in Germany in an aeroplane plant where eight men were employed in spraying a solution of cellulose acetate over the linen which covered the wings. Four of the men became jaundiced, and one died. This incident saved the Germans from serious trouble in aeroplane manufacture, for before the outbreak of war in 1914 they prohibited the use of this solvent in aeroplane doping.

In England the first cases came to light in November 1914, when 19 workers developed jaundice in an aeroplane works at Hendon. One man died after working for 11 weeks as a doper, and it was proved that his

death was due to tetrachlorethane (Willeox, 1915). The large number affected at the same time was due to the fact that a plenum system of ventilation was installed in the works and blew the heavy vapour into every corner of the large shed where the work was being done. Aeroplane works were springing up all over the country, overtime was being worked to the utmost, and all the dope used contained the noxious ingredient. Periodic medical examination at fortnightly intervals in the 50 or 60 factories was organized. Exhaust ventilation by fans which changed the air in the doping rooms 25 to 30 times an hour was insisted on, and alternation of employment was recommended. Conditions were ameliorated to such an extent that no outbreak affecting so large a number of workers in any factory occurred subsequently, but there were many isolated cases and deaths, and many workers continued to be suspended at the medical examinations.

Attempts to solve the problem by diminishing the quantity of tetrachlorethane in the dope failed, for even as little as 10 per cent. proved to be dangerous. Pressure was brought to bear to find a substitute for tetrachlorethane, and in July, 1917, the War Office and Admiralty were able to announce that no dope containing tetrachlorethane was being made or used. Seventy known cases of toxic jaundice with 12 deaths had been reported up to that time (Legge, 1917).

Two groups of cases of tetrachlorethane poisoning may be recognized in which the predominating symptoms are gastro-intestinal and nervous. Patients in whom nervous symptoms predominate usually, though not invariably, show no liver disturbance.

The course of the gastro-intestinal or hepatic form of the disease may be divided into four stages. In the first stage there is loss of appetite, fatigue, headache, vomiting, and abdominal pain occasionally so prominent as to suggest lead colic. In the second stage there is jaundice with clay-coloured stools and constipation. Most of the workers have to cease work at this stage through increasing fatigue. There may be a slight rise in temperature, vomiting, albuminuria, and even oedema of the legs. In the third stage the jaundice increases, the liver becomes enlarged and tender, and toxic symptoms appear. These include somnolence, delirium, convulsions, and coma, leading usually to death. The fourth stage is that of ascites, but death often occurs before this is reached. In fatal cases necrosis of the liver is found in the form of acute red and yellow atrophy. The organ is much reduced in size and may weigh 26 oz., or even only 19 oz. The kidneys may be pale, swollen, and fatty. Haemorrhages into serous membranes and the heart muscle may be present.

The nervous lesion is toxic polyn neuritis (Léri and Breitel, 1922). The illness begins with numbness and tingling of the fingers and toes. There is weakness of the interossei, and of the flexors and extensors of the fingers. Hypoaesthesia of the hands and feet is present, and sometimes tremor (Zollinger, 1931).

Polyneuritis has occurred especially in the artificial pearl industry, where the workers are exposed to tetrachlorethane not only by inhaling the vapour, but also in manipulating the liquid with their hands. Léri and Breitel have suggested that the lesion in the peripheral nerves may be a direct result of cutaneous absorption, since, in their series of cases, many who were exposed to the vapour suffered only from giddiness, while the two who showed polyneuritis developed it a month after first handling the liquid. Minot and Smith (1921) found that the blood changes in mild poisoning consist of an increase of large mononuclear cells up to 40 per cent., with a slight elevation of the white-cell count. Parmenter (1921) made routine blood counts in order to detect early poisoning among the workers in an artificial silk factory.

Amyl acetate can often be used as a solvent in place of tetrachlorethane. Closed apparatus should be used for cleaning purposes and adequate ventilation installed. Special precautions in the artificial pearl industry have been suggested in the form of glass cases with openings for the arms of the worker manipulating the pearls. Such a worker must wear rubber gloves. Prophylactic measures include removal of workers from exposure on the earliest appearance of anorexia, malaise, headache, constipation, drowsiness, or vomiting.

Trichlorethylene. Trichlorethylene is a colourless liquid with a faint aromatic odour. It is used for degreasing metals, in the extraction of oils and fats, in painting, enamelling, dyeing and dry-cleaning, in the boot and shoe industry, in textile manufacture and the printing industry, as an insecticide, a disinfecting agent, an impregnation material, in cleaning films, photographic plates, and optical lenses, in the chemical industry, in gas purification, and as a rubber solvent. In all these processes trichlorethylene may be used pure or as an addition to other solutions under various proprietary names, such as *benzinol*, *chlorylene*, *crawshawpol*, *dukeron*, *gemalgene*, *tetralene*, *trethylene*, *trielin*, *triklone*, *trilene*, *triol*, *tripur*, *vestrol*, and *westrosol*.

The outstanding result of animal experiments with trichlorethylene is the absence of any severe lesion of the liver and kidneys, such as is found with other halogenated hydrocarbons like tetrachlorethane. Only Castellino (1932) appears to have produced a slight fatty degeneration of the liver and granular degeneration of the kidneys in inhalation experiments.

There can be no doubt that the chief danger of trichlorethylene in industry is that of acute narcosis following prolonged exposure to high concentrations. Since 1935 it has been used as an inhalation anaesthetic and for this purpose resembles chloroform, but is less potent and less toxic (Hewer and Hadfield, 1941). Stüber (1931) recorded no less than 284 cases of poisoning from trichlorethylene, including 26 deaths, in German industry. She described the powerful narcotic effect of trichlorethylene, loss of consciousness having occurred in 117 cases. Twelve of the deaths occurred in men who failed to recover consciousness after prolonged exposure to a large

dose. Sometimes residual symptoms such as headache, giddiness, and loss of appetite occur, but it is difficult to decide whether these are not functional manifestations.

There is little evidence of the cumulative action of trichlorethylene, though it is possible that it has a special affinity for nervous tissue. Lesions of the second, fifth, and twelfth cranial nerves have been described, but there is some suspicion that they may have been due to an associated poison and not to trichlorethylene itself. Of Stüber's 284 cases, 10 showed fifth nerve paralysis and nine optic disturbances. These included blindness from optic atrophy in two cases, and retrobulbar neuritis with disturbances of the colour fields in the others. German factory inspectors have described corneal ulcer resulting from a foreign body in the eye, the workman not having been aware of its presence because of anaesthesia of the cornea.

Isenschmid and Kunz (1934) described the case of a man aged 56 years who had been exposed for a year to the vapour of trichlorethylene in the process of cleaning steel cylinders. He developed retrobulbar neuritis, accompanied by left-sided paralysis of the tongue and polyneuritis of all four limbs.

Trichlorethylene is less likely to attack the liver than tetrachlorethane, carbon tetrachloride, or chloroform. Toxic jaundice is recorded, but the evidence for attributing it to trichlorethylene itself is not definite. Stüber went so far as to state that the liver is never affected. Roholm (1933) stated that acute hepatitis may occur as late as 60 hours after the initial exposure and may produce acute necrosis of the liver like that due to delayed chloroform poisoning. Bridge (1933) reported the case of a boy who developed jaundice after six months' exposure to trichlorethylene in a degreasing process. There was a smooth enlargement of the liver, especially of the left lobe. Inquiry of the firm supplying the fluid precluded the possibility of tetrachlorethane having been substituted by mistake for trichlorethylene. Willcox (1934) described a case of toxic jaundice in a boy aged 16 years who had been employed dipping safety razor blades into a tub containing trichlorethylene. Before admission to hospital he had been jaundiced for a month and had frequently vomited. The temperature was normal and the liver enlarged. There was albumin in the urine. Gradually the jaundice cleared up and the liver became normal in size. The history and physical signs in these cases do not justify the conclusion that trichlorethylene was the causative agent to the exclusion of some other cause of jaundice.

Dermatitis was found by Stüber in 18 of her 284 cases, but she stated that in fact it was more frequent than this. It presented no special features, but like all dermatitis due to such substances was caused by the solvent action of trichlorethylene upon the fat in the skin.

Accidents with trichlorethylene occur under abnormal circumstances, such as cleaning out a sump without the fan running, or entering a cleaning apparatus without protection. When solutions containing trichlorethylene

are applied to the interior of closed vats, the men should work in pairs relieving each other frequently. The man in the enclosed space should be provided with a life-belt, and also with an apparatus through which he can breathe air from outside. Continued exposure to low concentrations of trichlorethylene causes a pleasant feeling of mild intoxication and may lead to a craving for further exposure. Such addiction was described by Baader in 1927 and has been frequently observed since. The use of capsules of trichlorethylene for trigeminal neuralgia is inadvisable. After its introduction about 1925 this mode of therapy remained popular for some time, but eventually proved disappointing. More recently it has been used to try to relieve anginal pain, but with a similar disappointing result.

Chlorinated naphthalene. When naphthalene is chlorinated a wax-like substance is produced. It is used in industry as an insulating coat on wires, or on metal bars to circumscribe the action of plating processes, for example, in chromium plating. The wax is usually melted in a bath and the articles may be dipped in the bath directly or the wax applied to them by means of a brush. Poisoning by chlorinated naphthalene may take the form of acne, particularly of the face, or of toxic jaundice produced by necrosis of the liver.

The typical skin condition starts on the face, around the angles of the jaws or over the malar prominences, and from there spreads on to the sides of the face and on to the sides and back of the neck. The skin lesions in a typical case are comedones, papules, pustules, and in severe cases small cysts. Sometimes the eruption spreads on to the shoulders and forearms.

The term ehlor-acne was first used by Herxheimer in 1899 to describe an eruption composed of comedones and small sebaceous pustules which occurred on the arms and faces of workers manufacturing ehlorine gas electrolytically, using carbon electrodes. It was natural to assume that the chlorine was the causative agent. Later, some authors suspected various ehlorobenzene derivatives such as hexa-ehlorobenzene, hexa-chlorethylene, para-nitrobenzene, perchloronaphthalene (*perna*), and probably others. Chlorinated naphthalene was first indicted by Wauer in 1918 as a cause of acneiform eruptions of the skin, the condition being called *Perna*krankheit. Workers engaged in the manufacture of this substance are exposed to fume of the molten mass and also to the sublimated dust. The majority of writers on the subject, particularly White (1934), have felt that ehlorine as such has little to do with the formation of the comedones and cysts, and they have repeatedly referred to tar and products of the distillation of tar as the prime causative factors. White rebuked authors for using the term ehlor-acne at all, and expressed the belief that the process is one of the manifold eutaneous reactions produced by tar and its derivatives. Jones (1941) pointed out that, in the absence of cleanliness, the chloronaphthalene irritates the sebaceous glands causing an excess of cell growth and secretion, followed by plugging of the glands and possible secondary infection. Cleanliness is, therefore, a most important factor.

Systemic effects from chlorinated naphthalenes were first pointed out by Lehmann in 1919. He found that animals which were fed on these substances, or inhaled them, lost appetite and at death showed liver lesions. Drinker, Warren, and Bennett (1937) administered chlorinated hydrocarbons by inhalation, subcutaneously and by mouth to white rats. Tri-, tetra-, penta-, and hexachloronaphthalenes and chlorinated diphenyl were used. These experiments showed that tri- and tetrachloronaphthalenes produced relatively unimportant pathological changes in the liver until extremely high concentrations were used. Animals exposed for six weeks to the higher chlorinations in relatively low concentrations regularly showed minor degrees of liver damage, even though, as a group, they gave no clinical evidences of such toxicity while alive. Exposed to still higher concentrations the rats lost weight and appetite and began dying after eight days of exposure, many with severe jaundice. Examination of the liver at necropsy revealed marked central fatty degeneration with necrosis of liver cells.

In 1936 three fatal cases of jaundice in chlorinated naphthalene workers were recognized in the United States of America (Flinn and Jarvik, 1936; Drinker, Warren, and Bennett, 1937). All three of the men were young and in none could any predisposing cause other than the industrial exposure be found to account for the illness. Two of the men who had worked side by side died within two months of each other. Both had been exposed to mixtures of penta- and hexachloronaphthalene, and one had been exposed to a mixture of tetra- and pentachloronaphthalene with 10 per cent. chlorinated diphenyl. In both, the diagnosis of acute yellow atrophy of the liver was made at necropsy. In the third case no necropsy was reported, but death occurred after an acute illness characterized by jaundice. In one case acne had preceded the jaundice. In addition to these fatal cases, Drinker, Warren, and Bennett also mentioned four cases of non-fatal jaundice among subjects with similar exposure. No details were given.

Greenburg, Mayers, and Smith (1939) recorded three fatal cases in young people working with chlorinated naphthalene and diphenyl. Two of the patients apparently had suffered from at least one previous attack of hepatitis, followed by a certain degree of improvement, before the fatal attack. McLetchie and Robertson (1942) and Collier (1943) recorded a fatal case in a woman of 41 years who worked in an engineering establishment in Scotland and was exposed to the fume and dust of chlorinated naphthalene. Necropsy showed acute red and yellow necrosis of the liver, which weighed 650 gm., the normal being 1,500 gm.

By attention to ventilation and medical supervision of workers the chlorinated naphthalenes and diphenyls can be handled in industry with safety. Education of the workers as to the cause of the acne must be undertaken and the necessity for personal cleanliness emphasized. Light coloured, highly starched, closely woven overalls with full length sleeves should be provided. These must be changed and laundered at least once a week. Adequate washing accommodation and locker space must be provided. The

work-people must be taught not to touch the skin with the hands and not to use rags for wiping the nose and the face. They must wash before meals and take food only in special rooms set aside for the purpose. Medical selection of workers must aim at avoiding adolescents and all persons with oily skins, established acne, or seborrhoea. Medical examination must be carried out at least once a week. All early cases of acne or jaundice must be removed from contact with the toxic substance. Prevention of systemic effects turns upon exhaust ventilation to remove fume and dust, and avoidance of over-heating of the wax.

THE GLYCOL GROUP

Since about 1925 a great new aliphatic chemical industry has grown up, which is already bigger than the coal-tar or aromatic industry. One result of this has been the introduction of a host of new solvents including ethylene chlorhydrin, dioxan, cellosolve, cellosolve acetate, methyl cellosolve, butyl cellosolve, carbitol, and butyl carbitol (Browning, 1937). The first two of these substances will be described since they have already caused poisoning in man. The others of the group may be toxic, too. Acute poisoning by ethylene chlorhydrin first attracted attention in a paper factory in Germany in 1927. Five deaths occurred in 1934 from exposure to diethylene dioxide in the manufacture of artificial silk in the Midlands.

Ethylene chlorhydrin. Ethylene chlorhydrin, also known as glycol chlorhydrin, is a clear, glycerine-like fluid with an odour like that of ethyl alcohol. Owing to its solvent action for cellulose acetate, resin, and wax, it is used in the lacquer industry especially as an addition to plasticizers for paint and varnish; also in the dyeing and cleaning industry, and in the linoleum, paper, and pharmaceutical industries.

Several cases of acute poisoning by ethylene chlorhydrin have been reported, three of them fatal. Chronic intoxication has not been observed. Two fatal cases, one in a paper factory and the other in a linoleum factory, were reported from Germany by Koelsch (1927). In the first case the workers cleaned the cylinder of a paper machine with cloths dipped in ethylene chlorhydrin. The symptoms began with nausea, vomiting, and drowsiness. Some hours later, severe headache and slight stupor developed, with vomiting. There was no fever, but râles were present in the lungs, and death occurred in syncope. At necropsy there was engorgement of the lungs and liver. The kidneys were unaffected. The case of the linoleum worker showed a latent period in the development of symptoms. The patient had slight vomiting and drowsiness in the morning and was then examined by a doctor who found nothing abnormal. In the afternoon, dyspnoea developed and he died the same evening. At necropsy there was oedema of the lungs and acute gastro-intestinal catarrh.

Middleton (1930) recorded a third fatal case occurring in England. Here the toxic effects appear to have been due not only to inhalation of the

vapour, but also to absorption through the skin, the patient having entered a still in a dye works to mop up water containing ethylene chlorhydrin in solution. The initial symptoms were vomiting and drowsiness. Death took place about 12 hours after removal from exposure. Necropsy showed oedema of the lungs and bronchopneumonia.

Sometimes nausea, vomiting, drowsiness, and weakness are followed by recovery after some days; many patients have no other symptom than slight irritation of the eyes (Koelsch, 1927). Both a large evaporation surface and increased volatilization through high temperatures must be forbidden. Since absorption can occur through the skin, contact with and splashing of ethylene chlorhydrin must be avoided.

Diethylene dioxide. Diethylene dioxide, or *dioxan*, is a colourless liquid with a faintly pungent odour. It is used as a degreaser, especially for wool, as a solvent in the textile, lacquer, and celluloid industries, and in the manufacture of polishes, pastes, cements, glues, shoe-creams, and cosmetics. In addition, it is a paint remover, preservative, fumigant, and deodorant.

In experiments carried out on guinea-pigs, Yant, Schrenk, Waite, and Patty (1930) were unable to demonstrate lesions of the kidneys or liver. Acute poisoning from the vapour caused irritation of eyes, nose, throat, and bronchi, and even necrosis. Their report suggests that owing to its low toxicity in small concentrations and its irritant effect, health hazards from breathing the vapour under ordinary conditions are slight.

Barber (1934) recorded the death of five men which occurred within a fortnight from exposure to *dioxan* in the manufacture of artificial silk in a works near Derby. The process on which they were employed had been in use for nearly 16 months, but for five weeks before they became ill, exposure to the vapour was intensified by the speeding up of the machine on which they worked. Diethylene dioxide is not highly volatile under ordinary conditions, but here the men found it necessary to put their heads into the vat containing the noxious substance. The premonitory symptoms were nausea, vomiting, and abdominal pain. In two cases an acute abdominal emergency was simulated. In no case was there jaundice to indicate necrosis of the liver. From about the third day of the illness the urine was scanty, and in one case it was found to contain blood and albumin. The symptoms of uraemia with suppression of urine were predominant after the first few days, and death occurred in about a week. In one case the blood-urea reached 346 mg. per 100 c.c. The blood counts in three cases showed no anaemia or change in the red cells, but the white-cell counts varied between 21,400 and 38,000 per c.mm., with a high percentage of polymorphs.

In the four cases submitted to necropsy the kidneys showed haemorrhagic nephritis with necrosis of the outer part of the cortex. There were areas of necrosis of the liver without bile staining or fatty change. Histologically there was complete necrosis of the inner half of each lobule. Absorption evidently occurred by inhalation, and the severity of the changes in the

kidneys suggests that death was due to the great increase of the dose which occurred when the process was intensified.

There was a possibility of exposure in 80 other men, and detailed inquiries showed that some of these had suffered from anorexia, nausea, and vomiting. No jaundice had been present in either the fatal cases or in exposed workers examined, but in one of the latter the liver was palpable and a trace of albumin and a few red blood-cells were found in the urine. There was also a trace of albuminuria in 65 per cent. of those much exposed and in 50 per cent. of the others.

Henry (1934) divided intoxication into three stages. The earliest effects include irritation of the nasopharynx with cough, of the nose with coryza, and of the conjunctivae with misty vision. Even if the inhalation is continued this irritation may subside and thus give rise to a false sense of security. Drowsiness, vertigo, headache, loss of appetite, nausea, and vomiting follow. If at this stage a rest of 24 hours is taken the ill effects tend to pass off quickly. In the second stage the gastric symptoms become more severe. There is pain and tenderness in the abdomen and lumbar region, and enlargement of the liver. After removal from exposure for a week or so these effects pass off gradually. In the third stage there is acute haemorrhagic nephritis which may lead to suppression of urine, uraemia, coma, and death.

In 1934 Fairley, Linton, and Ford-Moore exposed rats, mice, guinea-pigs, and rabbits over long periods to mixtures of *dioxan* and water in the approximate ratio of four to one. The animals inhaled the vapour in the form of a spray. Lesions were observed, sometimes of great severity, in the kidneys and liver. They were present even in animals exposed to a non-lethal concentration of 1 in 1,000 of the mixture.

Where the use of *dioxan* cannot be confined to enclosed apparatus adequate exhaust ventilation must be provided and large evaporation surfaces forbidden.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1943

THIRTY-SEVENTH ANNUAL GENERAL MEETING

THE THIRTY-SEVENTH ANNUAL GENERAL MEETING was held in London, at the London School of Hygiene and Tropical Medicine, on Saturday, 12 June, 1943. The attendance book was signed by 103 members. The proceedings began at 9.45 a.m.

The President, Professor J. A. Ryle, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Place of Meeting in 1944. It was suggested that it might be possible to hold the Meeting in Leeds or Sheffield. No information was available as to the possibility of providing accommodation in either place, and it was left to the Secretary to make inquiries. Opinion was divided on the advisability of holding a meeting lasting two days, and it was left to the Executive Committee to decide. The suggestion that a series of related clinical cases should be demonstrated met with general support.

The Treasurer presented the Annual Accounts, which were adopted. They showed a balance of £326.

Election of Officers

President. Major-General Sir Henry Tidy was elected President, and on taking the Chair expressed the thanks of the Association to the retiring President.

Election of Officers, Executive Committee, Extra-Ordinary Members, Honorary Member, and Ordinary Members then followed.

Executive Committee

President. Major-General Sir Henry Tidy.

Treasurer. Professor L. J. Witts.

Secretary. Dr. C. E. Newman.

Members for England:

Dr. T. Izod Bennett.
Dr. R. Clarke.
Dr. L. B. Cole.
Dr. J. L. Livingstone.
Dr. J. Parkinson.
Dr. J. C. Spence.

Members for Scotland:

Dr. J. Craig.
Professor G. B. Fleming.
Professor D. Murray Lyon.

Members for Ireland:

Dr. F. M. B. Allen.
Dr. G. C. Dockeray.
Dr. P. T. O'Farrell.

Honorary Member

Professor J. A. Ryle.

Extra-Ordinary Members

Dr. P. Hamill.
 Professor A. W. Harrington.
 Professor W. E. Hume.
 Dr. T. P. C. Kirkpatrick.
 Dr. C. McNeil.
 Professor L. G. Parsons.
 Professor A. Ramsbottom.
 Professor W. H. Wynn.

Ordinary Members

Thomas Anderson, F.R.C.P. (Ed.), Physician Superintendent, Knightswood Fever Hospital, Glasgow.
 Charles Nathaniel Armstrong, M.D., M.R.C.P., Physician, Royal Victoria Hospital, Newcastle.
 Macdonald Critchley, M.D., F.R.C.P., Physician, King's College Hospital.
 Alan Morton Gill, M.D., M.R.C.P., Assistant Physician, West London Hospital.
 Traugott Ernest Gumpert, M.B., M.R.C.P., Assistant Physician, Sheffield Royal Hospital.
 Douglas Hubble, M.D., Assistant Physician, Derby Royal Infirmary.
 Francis Avery Jones, M.D., M.R.C.P., Senior Physician, Central Middlesex County Hospital.
 Francis Frederick Kane, M.D., M.R.C.P. (I.), Medical Superintendent, Belfast Fever Hospital.
 Lawrence Martin, M.D., M.R.C.P., Physician, Emergency Medical Service.
 Harold Scarborough, M.B., M.R.C.P. (Ed.), Temporary Assistant Physician, Royal Infirmary, Edinburgh.

SCIENTIFIC BUSINESS

Saturday Morning

1. DR. N. S. ALLISON, illustrating *The Symptomatology of Peptic Ulcer*, presented a review of 131 clinical cases with the object of comparing clinical and radiological criteria of diagnosis. Unequivocal radiological evidence of ulcer was found in 51 cases or 39 per cent. (group A), doubtful evidence in 30 cases or 23 per cent. (group B), and the X-ray findings were negative in 50 cases or 38 per cent. (group C). Analysis on a statistical basis of groups A and C showed that while typical pain, food relief, night pain, remissions, hyperchlorhydria, under-nutrition, and the absence of gross anxiety or depression are valuable in diagnosis, and more common in cases with radiological evidence of ulcer, their preponderance in group A, as compared with group C, was not as great as might have been expected. Weighing the individual symptoms and plotting the scores graphically showed that there was considerable overlap of the two groups. Two possible explanations were considered (inadequate history-taking and simulation, and faulty X-ray technique), but it was suggested that the observations lent further support to the view that the ulcer was incidental and not essentially responsible for the symptoms of this common form of dyspepsia.

2. MAJOR-GENERAL SIR HENRY TIDY described *The Incidence of Peptic Ulcer, 1910 to 1938*. The crude death-rates per million living in England for peptic ulcer in males were constant from 1912 to 1921, rose rapidly between 1921 and 1930, and were constant again until 1938. This is substantially true for both gastric and duodenal ulcer, the rise being due to ages over 40 years. There was no rise for ages under 40, nor for females at any age. In 1938 the death-rate for London was twice that for Rural Districts. Admissions of males to St. Thomas's Hospital show a predominance of duodenal ulcer until 1926 and subsequently an increasing predominance of gastric ulcer.

These two communications were discussed by DR. IZOD BENNETT, SIR ARTHUR HURST, PROFESSOR RYLE, SIR ADOLPHE ABRAHAM, COLONEL MIDDLETON, and DR. PARKES WEBER.

3. DR. J. MCMICHAEL and PROFESSOR J. H. DIBLE (introduced) demonstrated *Biopsy Studies on Acute Hepatitis*. Histological sections were shown from cases of arsenotherapy jaundice, epidemic hepatitis, and jaundice following serum inoculations. In every instance there was an inflammatory lesion of the liver affecting the lobules either

diffusely or zonally. The processes of recovery were demonstrated. In diffuse lesions this could be rapid and dramatic; in zonal lesions recovery was much slower and had not been followed through to complete histological restoration of the liver. These cases often ran a grumbling course over many weeks, but with ultimate complete clinical recovery. The processes of transition to acute necrosis and chronic cirrhosis were also shown.

4. DR. J. B. RENNIE and DR. J. REID (introduced) discussed *Liver Efficiency Tests* in 80 patients with hepatic disease. Quick's oral hippuric acid test was positive in 86 per cent. A modified laevulose tolerance test was less sensitive. The response of the plasma prothrombin to parenteral injection of vitamin K was of practically no value in detecting liver damage. Changes in plasma albumin and globulin could not be definitely ascribed to liver injury. Both the two first-mentioned tests were useful in determining the course of acute infective hepatitis, but neither was helpful in differentiating one liver lesion from another.

These two communications were discussed by SURGEON REAR-ADMIRAL MCNEE, SIR PHILIP MANSON-BAHR, DR. PARKES WEBER, SIR ARTHUR HURST, COLONEL MONTGOMERY, LT.-GENERAL BIGGAM, PROFESSOR HIMSWORTH, DR. MALCOLM BROWN, and the PRESIDENT.

5. DR. ALICE M. STEWART (introduced by PROFESSOR L. J. WITTS) described *The Clinical Picture of Carbon Tetrachloride Poisoning*. A chemical process which involved continuous exposure to variable concentrations of carbon tetrachloride vapour had been carried out under specially difficult conditions of ventilation for two and a half years. During this time there had been an extremely high incidence of gastro-intestinal symptoms amongst the workers, and five cases of albuminuria had been discovered on routine examination. No deaths had occurred. Clinical examination of 70 workers was essentially negative, but the history was that of recurrent bouts of nausea, vomiting, abdominal pain, and diarrhoea, accompanied by a characteristic mental hebetude with loss of powers of concentration, sleep disturbances, and headache. A heightened sensitivity to the smell of the vapour resulted in an increased frequency of the attacks as time progressed, and residual effects such as persistent nausea, vague abdominal discomfort, and perversions of appetite gradually made their appearance. A striking gain in weight had occurred in most of the women and a few of the men during the early weeks of exposure.

Lunchcon

The Association then adjourned to luncheon at the Holborn Restaurant, where MAJOR-GENERAL SIR HENRY TIDY, in proposing the toast of the Association, welcomed the distinguished physicians from the Forces of the United Nations who were attending the meeting as guests, more particularly COLONEL MIDDLETON, the only member representing the American Association of Physicians, which was, in a sense, the parent body of this Association.

Afternoon Session

6. DR. F. H. KEMP described *The Radiographic Appearance of Carbon Tetrachloride Sickness*. He found an abnormal state of irritability of the stomach and intestine, of which the principal manifestations were spasm of the pylorus, and hypermotility and spastic movements of the small bowel and colon. Though not all persons were affected to the same degree, the reactions were essentially the same, though varied in intensity, and they persisted for many months after the gastro-intestinal upset.

PROFESSOR L. J. WITTS, in summing up this complete investigation on the workers, which had shown no evidence of disease of the liver, kidneys, or blood-forming organs, said it seemed unlikely, therefore, that the symptoms of chronic carbon tetrachloride poisoning were due to damage to these tissues, and he ascribed them to the direct action of carbon tetrachloride on the central nervous system and the alimentary tract.

These two communications were discussed by DR. HAMILL, PROFESSOR DAVIDSON, and PROFESSOR WILKINSON.

7. DR. WILLIAM EVANS discussed *Triple Rhythm*, the cadence produced when three sounds recurred in successive cardiac cycles. He described a classification for triple rhythm which was based on the position of the supernumerary sound in the cardiac cycle and on the disease causing it. There were three types. In the first variety (Type I), the third heart sound is added, and is found in health or in right heart failure

in mitral stenosis, hypertension, emphysema, congenital heart disease, and thyroid toxæmia. In the second variety (Type II), the fourth heart sound is added, and is found in delayed auriculo-ventricular conduction or in the left ventricular failure from hypertension or aortic incompetence. In the third and less important group (Type III), the extra sound occurs during systole and precedes the second heart sound; it is found in health. DR. EVANS emphasized the common incidence of triple rhythm and said that the appreciation of this would come to us just as soon as we habitually adopt self-catechism during clinical auscultation in terms of 'Do I hear more than two heart sounds?'

DR. BRAMWELL commented on DR. EVANS's communication.

8. DR. A. G. OGILVIE presented his *Observations on a Series of Asthmatic Patients*, a report on the study of 547 asthmatic patients observed during a period of 10 years. The object was the study of the individual asthmatic rather than of 'asthma'. It was found that in the majority of patients the symptoms were the result of a combination of factors, allergic and emotional, but that in many one or the other of these was the sole or predominant cause. Continuous asthma was found to be mainly emotional in origin in most cases, and among these were found the most severe of all. It was found that the allergic asthmatic attack was well controlled by adrenalin, but that non-allergic spasms were but slightly relieved. Three cases of adrenalin addiction were met with and it was urged that the self-administration of adrenalin should not be encouraged if injection by Hurst's method failed to produce definite relief in 15 minutes.

The Association then adjourned to tea at the London University Club, and on reassembling,

9. PROFESSOR H. COHEN with MR. J. PENNYBACKER and DR. D. RUSSELL (introduced) described *Precocious Puberty associated with a Cystic Astrocytoma involving the Third Ventricle and Right Temporal Lobe*, the clinical and pathological features presented by a boy of seven years with the genital and skeletal development of a youth of 15, but showing no intellectual precocity. There was well marked hydrocephalus, papilloedema, a left homonymous field defect, left hemiparesis, tremulous clumsy movements of the limbs, and unsteadiness of gait. Ventriculography revealed a tumour occupying the posterior part of the third ventricle and extending into the right temporal lobe. Outbursts of rage, hyperpyrexia, tachycardia, and tachypnoea were immediate pre-mortem features. Tapping the tumour revealed its cystic and gliomatous nature and at autopsy an extensive cystic astrocytoma was found involving the third ventricle, right temporal lobe, and hypothalamus, including the mamillary bodies, but the pineal body was normal. PROFESSOR COHEN discussed the problem of precocious puberty associated with gonadal, adrenal, thymic, and pituitary dysfunction. He doubted if the occasional association of precocious puberty with a tumour of the pineal body could be regarded as evidence of an incretory function of this structure; the available evidence pointed rather to the precocity depending on tumours or other lesions disturbing the functions of the posterior hypothalamic region, including the mamillary bodies.

DR. PARKES WEBER and DR. DOCKERAY discussed this communication.

10. DR. R. A. McCANCE and DR. E. M. WIDDOWSON (introduced) discussed *Growth at Home and at School*. The heights and weights of boys at two public schools had been subjected to analysis. The measurements had been made by the school authorities at the beginning and end of each term over a number of years. The monthly increments both of weight and height were always greater during the holidays than they were during the term. These findings confirm and extend those of Allan (1937, 1939).¹ The reasons for these artificial fluctuations in growth-rate are not at present known. They are probably nutritional in origin, although the boys at both schools were said to be well fed. They are possibly associated with increased exercise during the term without a corresponding increase in calorie intake. The problem should be susceptible to experimental solution.

This communication was discussed by DR. PARKES WEBER, DR. JENNER HOSKIN, DR. R. E. SMITH, DR. WARD, and the PRESIDENT.

11. DR. G. DONALDSON (introduced) described *A Study of Haemoglobin levels of 3315 Individuals in Edinburgh in 1942*. An investigation was carried out in Edinburgh in

¹ Allan, J. (1937) *Lancet*, I, 674; (1939) *Ibid.* I, 1300.

1942-3 into the haemoglobin levels of 3315 persons from birth to 54 years of age. The estimations were carried out under standard conditions with a Haldane haemoglobino-meter. Normal haemoglobin standards according to age and sex were discussed, the ranges accepted being considered to be average but not necessarily optimal. Haemoglobin figures 10 and 15 per cent. below these standards were taken as subnormal levels and levels of clinical anaemia respectively. On this basis, clinical anaemia was found to be present in 28 per cent. of infants and pre-school children, 39 per cent. of municipal school children, 12 per cent. of adolescent females, 7 per cent. of adult females, 24 per cent. of pregnant women, and less than 1 per cent. of adolescent and adult males.

PROFESSOR DAVIDSON, the PRESIDENT, and PROFESSOR WITTS commented on this study.

12. PROFESSOR NOAH MORRIS with DR. C. M. KESSON and DR. B. A. BALFOUR (introduced) discussed *Senile Osteoporosis—Incidence and Pathogenesis*. The incidence of osteoporosis was studied in a group of patients with ages varying from 50 to 93 years. The incidence was greater after the end of the seventh decade and in women, especially multiparae. Symptoms were not usually present unless some complications such as collapse of a vertebra had occurred. Blood chemistry was normal apart from a slight increase of plasma-phosphatase. The aetiology was discussed under the following headings: (1) Deficiency in diet, (2) Defective absorption, (3) Lack of exercise, (4) Presence of vascular disease, and (5) Hormonal dysfunction. Retention of calcium was high even after a period of 10 months on a high calcium intake, but no change was produced in the X-ray picture. No correlation could be detected between periods of inactivity and the presence of osteoporosis in senile subjects, but in patients with the post-encephalitic syndrome there appeared to be a significant correlation between the degree of helplessness and the presence of osteoporosis. No evidence was obtained that vascular disease or endocrine dysfunction played a part in the pathogenesis of generalized osteoporosis.

DR. GRAHAM, PROFESSOR HIMSWORTH, and PROFESSOR WITTS contributed to the discussion of this communication.

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